UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

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SUBJECT: **Coumaphos:** Draft Human Health Risk Assessment for Registration Review.

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This document provides the HED's human health risk assessment for the Registration Review of coumaphos (*O, O*-diethyl *O*-3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphorothioate). The most recent quantitative human health risk assessment was conducted in 2007 (D315769, K. Schumacher, 02/28/2007). The hazard characterization and endpoint selection were provided by Chris Schlosser; the residue chemistry assessment, dietary exposure assessments, and risk assessment were provided by Sheila Piper; the occupational and residential exposure assessment

were provided by Bridgett Bobowiec; and the drinking water assessment was provided by Faruque Khan of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Coumaphos is a broad spectrum organophosphate (OP) insecticide/acaricide used to control arthropod pests on beef cattle, dairy cows, goats, horses, sheep, swine and swine bedding. The chemical is also embedded into livestock ear tags and bee hive strips. There are currently no registered residential (non-occupational) uses for coumaphos.

Coumaphos is formulated as a technical 96% active ingredient (a.i.), as well as a dust formulation intermediate (25% a.i.), a dust (1% a.i.), an emulsifiable concentrate (6.15 and 11.6 % a.i.), and a flowable concentrate (42% a.i.). Coumaphos is also embedded into cattle ear tags, (20% a.i) and bee hive pest control strips (10% a.i). The bee hive pest control strips can be applied year around, including during honey flow (honey accumulation) and can remain in the hive for up to 45 days. The application of coumaphos to livestock can include use of the following equipment: swim and hydraulic dip vats, shaker cans, dust bags, back oilers/rubbers, mechanically and manually pressurized handguns, backpacks, and ear tags. Use of coumaphos in dip vats to control pests on cattle livestock is limited to employees of the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) and are enrolled in a cholinesterase monitoring program. Mechanical dusting is prohibited and there are label restrictions on the number of livestock and area per day. Applicators are restricted to spraying no more than 100 animals in one day at maximum application rate and 200 animals a day at one half the maximum application rate. In addition, applicators are limited to dusting no more than 25 animals in one day and no more than 1,000 square feet of swine bedding in one day.

Coumaphos, like other OPs, binds to and phosphorylates the enzyme, acetylcholinesterase (AChE), in both the central brain and peripheral nervous systems leading to accumulation of acetylcholine and, ultimately, to clinical signs of toxicity. Coumaphos requires metabolic activation of the oxon metabolite to inhibit AChE. For coumaphos, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. OPs also exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. Therefore, steady state exposure assessments of 21 days and longer were conducted instead of the traditional short and intermediate term assessments.

The toxicology database for coumaphos is complete, with the exception of a subchronic inhalation study and a coumaphos oxon comparative cholinesterase assay (CCA) study. HED's Hazard Science Policy Council (HASPOC) determined, based on a weight of evidence (WOE) approach that a subchronic inhalation toxicity study is required for coumaphos due to unacceptable inhalation risk estimates using the current point of departure (PoD) from an oral study. The toxicological PoDs are based on the results of benchmark dose (BMD) analyses where appropriate, and WOE consideration of all reliable data. A PoD for the acute dietary (all populations) exposure scenario was derived from the results of an acute CCA rat study conducted with coumaphos. A benchmark dose lower limit for 10% response ($BMDL_{10}$) of 0.19 mg/kg/day associated with RBC ChE inhibition in adult males was selected. No sensitivity was observed to PND 11 pups following acute exposure. Therefore, this BMDL10 is protective of RBC AChE inhibition in PND11 pups, as the BMDL10 for pups was 0.25 mg/kg. A PoD for the steady state dietary (all populations) exposure scenario was derived from the results of a 2

generation rat reproduction study. The $BMDL_{10}$ is 0.04 mg/kg/day for RBC ChE inhibition in both sexes of the F0 and F1 generations. The acute and steady state PoDs are based on the most sensitive $BMDL_{10}$s for RBC AChE (the most sensitive compartment), and thus are protective of the observed sensitivity of juvenile rats following repeated exposure.

Coumaphos requires bioactivation to the oxon to allow AChE inhibition; however, no data were submitted regarding the toxicity of the oxon. Although oxon CCA data are not available for coumaphos, EPA plans to move forward with the coumaphos human health risk assessment without toxicity data for coumaphos's oxon degradate. Due to the lack of coumaphos-specific oxon CCA data, EPA has used an oxon toxicity adjustment factor of 50X in its calculations (See Section 4.6.2). Also, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor (10X) for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios. Additionally, there is a data gap for coumaphos for a subchronic inhalation study. Therefore, a total database uncertainty factor of 30X, to account for the uncertainty in the human dose-response relationship for neurodevelopmental effects and the lack of an inhalation study, will be used for coumaphos for the population subgroups that include infants, children, youth, and women of childbearing age for inhalation exposure scenarios.

Coumaphos is classified as "not likely to be carcinogenic in humans" based on lack of evidence of carcinogenicity in rats and mice. A quantitative cancer risk assessment is not required.

The existing residue chemistry database for coumaphos is adequate for risk assessment purposes. The residue of concern in plants and animals for both tolerance expression and risk assessment includes coumaphos and its oxygen analog, coumaphoxon. The residue of concern for risk assessment purposes in drinking water is coumaphos and coumaphoxon. The Environmental Fate and Effects Division (EFED) performed surface water and groundwater modeling using the highest application rates. The highest estimated drinking water concentrations were from surface water modelling. The drinking water assessment assumed that during a rain event, coumaphos wash-off from treated cattle can be potentially adsorbed into manure as well as transported as effluent from concentrated animal feeding operations and pasture/rangeland.

The acute and steady state dietary exposure and risk assessment incorporated PDP monitoring data for honey, milk and livestock commodities, assumes a 50x toxicity adjustment factor (TAF) for coumaphoxon in drinking water only, DEEM default processing factors, and assumed all hives and livestock are treated (100% crop treated (CT)). Acute assessments exposure estimates are below HED's level of concern (LOC; <100% of the acute population adjusted dose (aPAD)) for the U.S. population and all population subgroups. The food only dietary exposure estimate is 50% of the acute population adjusted dose (aPAD) for the U.S. population, and 98% of the aPAD for children 3-5 years old, the most highly exposed population subgroup at the 99.9^{th} percentile. Combined dietary exposure from food and drinking water at the 99.9^{th} percentile of exposure is 51% of the aPAD for the U.S. population and 99% of the aPAD for children 3-5 years, the most highly exposed population subgroup.

Steady-state assessments were conducted in the DEEM acute module using the steady-state endpoint, monitored food residues, and 21-day rolling water averages to provide an estimate of

21-day ("steady-state") average daily exposures. Steady-state assessments exposure estimates are above HED's LOC (>100% of the steady state population adjusted dose (ssPAD)) for the U.S. population and all population subgroups, except adults 50-99 years old. The food only dietary exposure estimate is 210% of ssPAD for the U.S. population, and 380% of the ssPAD for children 1-2 years old, the most highly exposed population subgroup at the 99.9th percentile. Combined dietary exposure from food and drinking water is 210% of the ssPAD for the U.S. population and 390% of the ssPAD for children 1-2 years, the most highly exposed population subgroup. Beef meat is the risk driver when combining food in the steady state assessment for coumaphos, accounting for approximately 90% of estimated exposure in the dietary assessment based upon critical exposure contribution analysis.

There are currently no registered uses of coumaphos in or around residences; therefore, risk assessments for residential (non-occupational) exposure are not warranted at this time. A non-occupational bystander spray drift assessment was not performed for coumaphos at the time because of the limited use pattern on livestock.

The acute and steady state aggregate assessment for coumaphos includes only food and water exposures. Residential aggregate exposure assessments are not required since none of the currently registered uses result in residential exposure. Because coumaphos has been classified as a "not likely human carcinogen", a cancer aggregate risk assessment is not required.

Occupational exposure is possible with use of products containing coumaphos applied as both liquid sprays/solutions and as solids. The "steady state" endpoint selection for coumaphos overlaps with HED's traditional short-term exposure duration endpoint selection and is considered health protective for occupational handlers that apply commercially over longer periods of time (i.e., intermediate-term exposures). Chronic exposure is not expected for the registered uses.

Based on the use patterns of coumaphos, there are eight major handler exposure scenarios assessed in this memorandum: mixing/loading liquids for hydraulic type dip vats; mixing/loading liquids for swim type dip vats; mixing/loading liquids for back rubber/oilers; loading dust into bags; applying dusts with a shaker can to livestock or swine bedding; mixing/loading/applying liquids for backpack, mechanically pressurized handguns, and manually pressurized hand-wands. Exposure to applying ear tags and bee hive control strips were not quantitatively assessed.

Personal protective equipment, or PPE, mandated on coumaphos labels varies depending on the type of formulation (liquid or dust) and maximum application rate. Coumaphos labels require gloves for handlers however respirator requirement is inconsistent across labels. A total aggregated risk index (ARI) was used as a risk metric to account for the different LOCs between dermal (LOC = 1,000) and inhalation (LOC = 3,000) exposure. Occupational exposure scenarios for all formulations types and application rates were of concern (ARIs < 1) at both label required PPE and additional mitigation PPE levels. The one exception of this was mixing and loading liquid products EPA registration numbers 11556-115 and 11556-23 for livestock back oil rubbers (ARI = 1 with double layer dermal protection and PF5 respirator).

A quantitative dermal post-application exposure was not conducted for coumaphos uses. The amount of dermal exposure to post-application workers is likely to be substantially lower than the exposure to handlers, therefore, the handler assessment would also be protective of risks to post-application workers. In addition, coumaphos labels include the language, "Do not contact treated animals until sprays have dried and dusts have settled on the coat."

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for coumaphos at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for coumaphos.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from Pesticide Handler Exposure Database (PHED) 1.1; and the Agricultural Handlers Exposure Task Force (AHETF) database; submitted to the Agency by the registrant are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 HED Recommendations

2.1 Data Deficiencies

The database of toxicology studies for coumaphos is complete, with the exception of a subchronic inhalation study and a coumaphos oxon comparative cholinesterase assay (CCA) study.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical

For the purpose of registration review, adequate methods are available for the enforcement of the established tolerances for residues in/on honey and honeycomb. Adequate LC/MS/MS methods (Bayer Methods 75043 and 75044) are available for enforcing tolerances for coumaphos and its oxygen analog (coumaphoxon, also referred to as coumaphos-PO) residues in honey and beeswax. Additionally, the FDA multi-residue methods are also adequate for determining residues of coumaphos and its oxygen analog in honey. It is not known whether the methods are adequate for determining either coumaphos or its oxygen analog in beeswax (honeycomb).

[1] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

For the purpose of registration review, an adequate method is available to enforce the established milk and livestock tolerances. The GC-NPD enforcement method 74310 adequately recovers residues of coumaphos and coumaphoxon from milk and livestock tissues.

2.2.2 International Harmonization

There are currently no Mexican or Codex maximum residue limits (MRLs) for coumaphos; there are Canadian MRLs set at 0.5 mg/kg (calculated on the fat content) for coumaphos (defined as coumaphos, *per* se) in meat, meat byproducts, and fat of cattle, goats, horses, hogs, poultry, and sheep. The U.S. tolerances for residues in livestock commodities are set at 1.0 ppm to account for the parent and its oxygen metabolite at the limit of quantitation (LOQ). A Canada MRL of 1.0 ppm was proposed based on the method limit of quantitation for beeswax. A U.S. tolerance is based on the use of coumaphos-impregnated strips in beehives, and HED recommends in favor of the establishment of permanent tolerances for the combined residues of coumaphos and its oxygen analog at 0.15 ppm in honey, and 45 ppm in honeycomb. A U.S. tolerance on honeycomb adequately covers beeswax; therefore, a tolerance was not recommended for beeswax. Refer to Appendix B.2 for complete summary of international tolerances.

2.2.3 Recommended Tolerances

Permanent tolerances have been established in 40 CFR §180.189 for the combined residues of coumaphos (*O,O*-diethyl *O*-3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphorothioate and its oxygen analog (*O,O*-diethyl *O*-3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphate). The established tolerances shown below have not be changed and only the tolerance expression should be revised.

The tolerance expression for coumaphos has been reviewed and should be updated as follows based on HED's Interim Guidance on Tolerance Expressions (S. Knizner, 5/27/09).

> Tolerances are established for residues of the insecticide coumaphos, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of coumaphos (0,0-diethyl 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) phosphorothioate) and its oxygen analog (0,0-diethyl 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphate, calculated as the stoichiometric equivalent of coumaphos.
>
> | | |
> |---|---|
> | Honey | 0.15 ppm |
> | Honeycomb | 45 ppm |
> | Cattle, fat | 1.0 ppm |
> | Goat, fat | 1.0 ppm |
> | Hog, fat | 1.0 ppm |
> | Horse, fat | 1.0 ppm |
> | Sheep, fat | 1.0 ppm |
> | Cattle, meat | 1.0 ppm |
> | Goat, meat | 1.0 ppm |

Hog, meat ..... 1.0 ppm
Horse, meat ..... 1.0 ppm
Sheep, meat ..... 1.0 ppm
Cattle, byproducts ..... 1.0 ppm
Goat, byproducts ..... 1.0 ppm
Hog, byproducts ..... 1.0 ppm
Horse, byproducts ..... 1.0 ppm
Sheep, byproducts ..... 1.0 ppm
Milk Fat ..... 0.5 ppm

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

None

2.3.2 Recommendations from Occupational Assessment

A summary of the risk estimates have been provided, and shows that there are risk estimates of concern for registered uses of coumaphos based on the label-required personal protective equipment for occupational workers. Mechanical dusting is prohibited yet appears on some of the dust formulated labels (Co-Ral Bulk Dust (1%) [34704-267, and Co-Ral (1%) [960-184]. Label corrections/revisions should be made to remove all mechanical dusting and inconsistent respirator requirements including the TC21C respirator nomenclature.

HED continues to recommend that registrants submit more information on quarantine dipping practices to comply with 40 CFR 158.1070 post-application guidelines including use pattern information (e.g., cattle dipped per day, number of days dipping takes place per year, and etc.) in order to clarify and refine exposure scenarios.

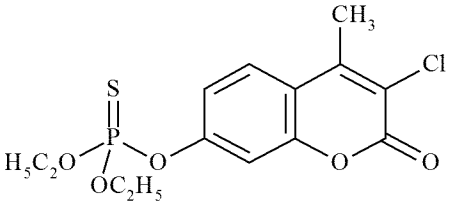
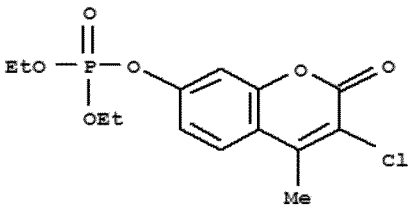
2.3.3 Recommendations from Residential Assessment

None

3.0 Introduction

3.1 Chemical Identity

Coumaphos is an organophosphate insecticide/acaricide currently used for the control of mites and insects on livestock. The chemical structure and nomenclature of coumaphos are presented in Table 3.1.

Table 3.1. Coumaphos Nomenclature.	
Chemical Structure	
Common Name	Coumaphos
Molecular Formula	$C_{14}H_{16}ClO_5PS$
Molecular Weight	362.78
IUPAC Name	*O*-3-chloro-4-methyl-2-oxo-2*H*-chromen-7-yl *O,O*-diethyl phosphorothioate
CAS Name	*O*-(3-chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl) *O,O*-diethyl phosphorothioate
CAS Registry Number	56-72-4
Chemical Class	Organophosphate
Coumaphos-oxon	
Molecular Formula	$C_{14}H_{16}ClO_6P$
Molecular Weight	346.7
CAS Name	0,0-diethyl 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphate
CAS Registry Number	321-54-0

3.2 Physical/Chemical Characteristics

The physiochemical properties of coumaphos are summarized in Appendix B.1. Technical coumaphos is a grey to tan powder with a slight sulfur odor. Volatilization from moist and dry soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 3.1 X 10^{-8} atm-cu m/mole and this compound's vapor pressure (9.7 x 10^{-8} mm Hg), respectively. Although it is stable in water, coumaphos hydrolyzes slowly in alkaline conditions. If released into water, coumaphos is expected to adsorb to suspended solids and sediment in water based upon the estimated Koc (1874-10297 L/kg

3.3 Pesticide Use Pattern

Coumaphos is formulated as a technical 96% active ingredient, (a.i.) as well as a dust formulation intermediate (25% a.i.), a dust (1% a.i.), an emulsifiable concentrate (6.15 and 11.6 %a.i.), and a flowable concentrate (42%a.i.). Coumaphos is also embedded into cattle ear tags, (20%a.i.) and bee hive pest control strips (10%a.i.). Multiple applications to livestock and/or livestock areas are permitted during a one year period. There are, however, label restrictions on the amount of livestock and livestock area treated per day. Applicators are restricted to spraying no more than 100 animals in one day at maximum rate or 200 animals a day at half of the maximum rate. There are also limits on dusting no more than 25 animals in one day and applying coumaphos to no more than 1,000 square feet of swine bedding in one day.

Application of coumaphos to livestock can include the use of the following equipment: swim and hydraulic dip vats, shaker cans, dust bags, back oilers/rubbers, mechanically and manually pressurized handguns, backpacks, and ear tags. Application rates range from 0.005 to 0.025 lbs a.i. per gallon for sprays or dips, 0.076 lbs a.i. per gallon of oil for back-rubbers, 0.000625 to 0.013 lbs a.i. per animal for dust application, and 0.000042 lbs a.i. per 1000 square feet of swine bedding treatment.

Labels vary considerably with respect to requirements for work attire and personal protective equipment (PPE). The product Co-Ral Flowable, EPA registration number 11556-98, which has the highest maximum spray application rate requires single layer dermal attire with the addition of gloves and a PF10 respirator. This product is restricted to employees of the USDA-APHIS[2] who are enrolled in the USDA-APHIS cholinesterase monitoring program. The USDA's Cattle Fever Tick Eradication Program (CFTEP) uses this product solely in Texas. The products EPA registration numbers 11556-115 and 11556-23 have lower spray application rates however do not require respirators for handlers. The dust coumaphos formulations products require dermal baseline attire (long sleeved shirt, pants, shoes and socks) along with gloves and at least a PF5 respirator. Table 3.3 provides a summary of the registered uses of coumaphos for each of the formulated products sorted by livestock type.

[2] APHIS- Animal and Plant Health Inspection Service

Table 3.3. Summary of Directions for Use of Coumaphos.

Application Timing, Type, and Equip.	Formulation (% ai.) [EPA Reg. No.]	Maximum Application Rate	Max. No. Application per Season	Max. Application Rate or Treatment Interval	Use Directions and Limitations
Cattle/Horses					
Swim Dip Vat Cattle only	Co-Ral Flowable Concentrate (42%) [11556-98]	0.025 lbs ai/gallon of spray	2 times/year	Do not make applications less than 10 days apart.	RUP[1] and use is restricted to employees of the USDA APHIS[2] who are enrolled in the USDA-APHIS cholinesterase monitoring program. For beef and non-lactating dairy cattle and horses. Charge dip vats with concentration of product and volume of water. Do not tip excessively thirsty animals. Applicators using handheld sprayers are limited to 100 animals are day at maximum application rate and 200 animals a day at ½ the maximum application rate. Apply as high pressure spray to wet the skin to run-off. Repeat applications as necessary. Respirator requirement.
Hydraulic Dip Vats Cattle only					
Manual and Mechanical Spray Cattle and Horses		0.021 lbs ai/gallon of spray	6 times/year		
Manual and Mechanical Spray Cattle and Horses	Co-Ral Fly and Tick Spray (6.15%) [11556-115], And Co-Ral Emulsifiable Livestock Insecticide (11.6%) [11556-23]	0.01 lbs ai/gallon of spray	6 times/year	Do not make applications less than 10 days apart. Re-treatment only necessary when insects reappear.	11.6 % is a RUP. Lactating and young cattle are subject to lower application rates. Do not apply rate above 0.0025 lb ai/gallon within 14 days of freshening. Do not apply on animals less than 3 months old. Do not spray animals for 10 day before shipping or weaning. Label limits handler to 100 applications to cattle a day and 200 a day if treated at ½ the maximum application rate. Apply for complete wetting to run-off. Do not contact treated animal until coats are dry. Do not spray in confined area. Do not use in conjunction with other OPs.
Back Rubbers Oil Cattle	Co-Ral Fly and Tick Spray (6.15% ai) [11556-115], And Co-Ral Emulsifiable Livestock Insecticide (11.6%) [11556-23]	0.076 lbs ai/ gallon of fuel	unknown	Re-treatment only necessary when insects reappear and constitute a problem.	For dairy cattle suspend at height that will prevent straddling. No interval needed between treatment and slaughter or use of milk. Back rubber application for horn files and face flies. Mix specified dosage in 1 gallon of No. 2 fuel oil. Hang so no dairy cattle can straddle. No interval required between treatment and slaughter or milk use.
Dust Bags and Shaker Can Cattle, Horses, Swine, Swine Bedding	Co-Ral Animal Insecticide (1%) Bulk Dust [11556-14], Co-Ral Shaker Can (1%) [11556-4], Co-Ral Bulk Dust (1%) [34704-267], Shaker Duster (1%) [69208-1] Y-Tex Co-Ral (1%) [39039-15], D- Louse (1%) [34704-306], Diolice (1%) [2393-378], Co-Ral (1%) [960-184], Zipcide Dust Bag (1%) [960-169]	0.125 lbs ai/bag 0.0013 lbs of ai/cattle	Shaker can: 12 times/year cows 6 times/year horses unknown	10 days apart. No interval required between treatment and slaughter or between treatment and use of milk.	Mechanical dusters are prohibited. For lactating dairy cows suspend bags in exit of milking barn. Limit number of animals can treat/day to no more than 25 animals and 1,000 feet of swine bedding. One 12.5 lb duster per 25 animals. For direct application by shaker can animals dusted using no more 2 oz. of dust per animal. PPE baseline plus gloves.

Table 3.3. Summary of Directions for Use of Coumaphos.					
Application Timing, Type, and Equip.	**Formulation (% ai.) [EPA Reg. No.]**	**Maximum Application Rate**	**Max. No. Application per Season**	**Max. Application Rate or Treatment Interval**	**Use Directions and Limitations**
Ear Tags Beef and Non Lactating Dairy Cattle	Corathon (15%) [11556-148], And Co-Ral Plus Insecticide Cattle Ear Tag (20%) [11556-123]	20%a.i., 15%	Replace as necessary		0.5 oz (14 grams) per tag. Wear chemical resistant glove when applying tags. All mature animals should be tagged. Attach one tag to each ear. Do not use on cattle less than 3 months old. Remove tags at end of fly season prior to slaughter.
Swine					
Shaker Can	Co-Ral Emulsifiable Livestock Insecticide (11.6%) [11556-14], Co-Ral Shaker Can (1%) [11556-4], Co-Ral Bulk Dust (1%) [34704-267], Shaker Duster (1%) [69208-1], Y-Tex Co-Ral (1%) [39039-15], D- Louse (1%) [34704-306], Diolice (1%) [2393-378], Co-Ral (1%) [960-184]	0.000625 lbs ai/pig	6 times a year	Do not make applications less than 10 days apart.	Mechanical dusters are prohibited. Limit number of pig can treat per day to 25. Do not enter allow contact with animals until dust has settled.
Mechanical and Manual Spray	Co-Ral Fly and Tick Spray (6.15% ai) [11556-115], and Co-Ral Emulsifiable Livestock Insecticide (11.6%) [11556-23]	0.005 lbs ai/ gallon of spray	6 times a year	Do not make applications less than 10 days apart.	Label limits handler to 100 applications to swine a day at maximum application rate. Do not contact treated animal until coats are dry. Do not spray animals for 10 days before shipping or weaning. Do not spray in confined area. Do not use in conjunction with other OPs.
Swine Bedding					
Shaker Can	Co-Ral Emulsifiable Livestock Insecticide (11.6%) [11556-14], Co-Ral Bulk Dust (1%) [34704-267, Shaker Duster (1%) [69208-1], D- Louse (1%) [34704-306], Diolice (1%) [2393-378], Co-Ral (1%) [960-184]	4.5×10^{-5} lbs ai/ft^2	6 times a year	Do not make applications less than 10 days apart.	Apply 2 oz. uniformly over 30 square feet of fresh dry bedding. Limit area of swine bedding treated per day to 1000 ft^2.
Bee Hives					
Bee Hive Strips	Checkmite + Bee Hive Pest Control Strip (10%ai) [11556-138]	10%ai by weight	Twice a year for Varroa mites and no more than four times for small hive beetle.		Leave strips in hive for at least 42 days but not over 45 days.

1 Restricted Use Pesticide (RUP)

2 U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS)

3.4 Anticipated Exposure Pathways

The Pesticide Re-Evaluation Division (PRD) has requested an assessment of human health risk to support the registration review of all existing registered uses of coumaphos. Humans may be exposed to coumaphos in food since coumaphos may be applied directly to animals resulting in secondary residues in milk and livestock commodities for human consumption and may be used in strips in hives resulting in residues in honey and honeycomb. Additionally, humans may be exposed to coumaphos in drinking water since coumaphos wash-off from treated cattle can come into contact with and be adsorbed onto manure as well as transported as runoff, reaching surface and ground water sources of drinking water. There are no residential uses of coumaphos, so there is not likely to be exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational post-application exposure is not expected due to the use pattern on livestock and embedded product formulations for ear tags and beehive strips. This risk assessment considers all of the aforementioned exposure pathways based on the existing uses of coumaphos.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled from the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Coumaphos is a member of the organophosphate class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP), also often called the mode of action (MOA), for coumaphos involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to

accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). Coumaphos requires metabolic activation to the oxon metabolite to inhibit AChE. For coumaphos, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating this toxicology database.

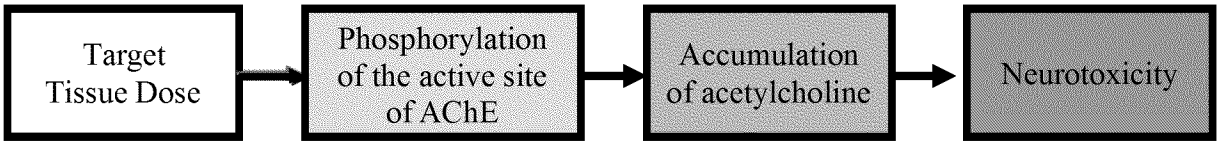


Figure 1. Adverse outcome pathway for OPs

4.1 Toxicology Studies Available for Analysis

The toxicology database for coumaphos is complete, with the exception of a subchronic inhalation study and a coumaphos oxon comparative cholinesterase assay (CCA) study. The Health Effect Divisions (HED's) Hazard Science Policy Council (HASPOC) determined, based on a weight of evidence (WOE) approach that a subchronic inhalation toxicity study is required for coumaphos due to unacceptable inhalation risk estimates using the current PoD from an oral study (April 29, 2013, TXR 0056625). Coumaphos requires bioactivation to the oxon to allow AChE inhibition; however, no data were submitted regarding the toxicity of the oxon. Although oxon CCA data are not available for coumaphos, EPA plans to move forward with the coumaphos human health risk assessment without toxicity data for coumaphos's oxon degradate. In lieu of coumaphos-specific oxon CCA data, EPA has used an oxon toxicity adjustment factor of 50X in its calculations. This value considers the data derived toxicity adjustment factor (TAF) that EPA has identified among oxon metabolites for other organophosphates, with an additional margin of safety included due to the uncertainty in extrapolating oxon potency data across chemicals (See Section 4.6.2 for details). The toxicology database includes the following toxicity studies:

- subchronic oral toxicity studies in rats,
- chronic oral toxicity studies in rats and dogs,
- carcinogenicity studies in rats and mice,
- developmental studies in rats and rabbits,
- reproduction study in rats,
- acute and subchronic neurotoxicity studies in rats,
- developmental neurotoxicity (DNT) study in rats
- acute and repeated comparative cholinesterase (ChE) studies in juvenile and adult rats,
- repeated, gestational ChE study in pregnant rat and fetuses,
- delayed neurotoxicity study in hens,
- 2, 5 and 21 day dermal toxicity in rats,
- immunotoxicity study in rats,
- complete mutagenicity study battery, and

- metabolism study in rats.

4.2 Absorption, Distribution, Metabolism, & Excretion (ADME)

Coumaphos, like some other OPs, requires metabolic activation to the oxon metabolite to inhibit AChE, with subsequent metabolism that leads to detoxification. Following oral administration, coumaphos was rapidly absorbed and eliminated in urine and feces with no evidence of bioaccumulation.

In a metabolism study, rats were administered [^{14}C] coumaphos as a single dose at levels of 1 mg/kg intravenously, and 1 and 15 mg/kg orally (MRID 00138596; Accession No. 25227074). A fourth group received 1 mg/kg coumaphos by the oral route daily for 14 days.

Following oral administration, the plasma half-life ranged from 2.35 to 3.3 hours at 1 mg/kg and 2.93 and 5.3 hours at 15 mg/kg (includes both single and repeated dose groups). Oral absorption was estimated to be 80% and 90% for the 1 mg/kg/day groups (single and repeat dosing, respectively), and 50% for the 15 mg/kg/day group. Urinary excretion was rapid with 63%-87% of the administered dose being excreted within 24 hours. For both doses, 76-96% of the administered dose was excreted within 168 hours following a single exposure. Tissue residues were highest in fat, kidney, liver and muscle. The urine contained 5 to 8 metabolites and the feces contained 5 to 7 metabolites. The major metabolite is chlorferon (dephosphorylated coumaphos). Coumaphos represented 0.1% of the urinary metabolites. Coumaphos represented 0.2% of the fecal metabolites when administered intravenously. However, when administered orally, coumaphos represented approximately 15 to 55% of the fecal metabolites. The range varies depending on whether coumaphos was administered as a single dose or as repeated doses. Sex differences were observed that suggest less complete oral absorption of coumaphos in female rats following single or repeated doses. Sex differences were not noted in high dose rats (15 mg/kg).

4.2.1 Dermal Absorption

There are no dermal absorption studies available. However, a dermal absorption factor is not needed for coumaphos because a route-specific dermal toxicity study was used to assess dermal exposure scenarios (see Section 4.5).

4.3 Toxicological Effects

Coumaphos is an OP with a neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes and life stages, and is being used in deriving PoDs. Coumaphos has quality dose response data across multiple life stages, durations, and routes for both RBC and brain AChE inhibition. Many of these studies have been evaluated using benchmark dose (BMD) modeling techniques. Based on Table 4.3.2.1, and Tables 2.1.1-2.2.2 in Appendix A2, RBC AChE inhibition is substantially more sensitive than brain AChE inhibition for all life stages evaluated (adults, juveniles, pregnant dams, and fetuses) in oral and dermal studies. Available studies with adult animals show similar findings in gavage and dietary studies. All of the oral studies modeled for BMD analysis were based on dietary administration except for the acute and 11 day

repeat CCA studies, which were based on gavage administration. Studies for the dermal route are available for route-specific evaluation. As mentioned previously, inhalation studies are not available for coumaphos.

No sensitivity to coumaphos was observed in developmental and reproduction guideline studies or following acute exposure in the CCA study. However, brain AChE (approximately 4-fold) and RBC AChE inhibition (approximately 2-fold) were more sensitive in PND 11 pups following repeated exposure in the CCA studies. Following gestational exposure, no fetal sensitivity was observed. However, in both the CCA and DNT studies, pregnant animals were approximately 2-fold more sensitive than non-pregnant females in repeat exposure studies. No sex-specific differences were observed at doses relevant for risk assessment. However, at higher doses adult female rats appear to be more sensitive than male rats.

Clinical signs of neurotoxicity can be found throughout the database of experimental toxicity studies at doses higher (10-fold) than those causing inhibition of AChE. In the subchronic neurotoxicity study, neurobehavioral effects such as decreased open field activity in males and decreased forelimb grip strength in females were observed. In the developmental studies, tremors were observed in maternal rats, and cholinergic signs and mortality (2/17 rabbits) were noted in maternal rabbits.

In acute lethality studies, coumaphos is highly toxic (Category I for the oral route and Category II for the inhalation route). Coumaphos is Category III for dermal toxicity, and is Category IV for eye and dermal irritation. It is not a dermal sensitizer.

Coumaphos requires bioactivation to the oxon to allow AChE inhibition; however, as stated above, no data were submitted regarding the toxicity of the oxon. In the absence of oxon toxicity data, exposure to coumaphos oxon is considered to be 50X as toxic as exposure to the parent (See Section 4.6.2 for details).

4.3.2 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined, and focused on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute, single dosing, and repeated dosing studies in laboratory animals. This analysis provides the basis for determining which exposure durations are appropriate for assessing the human health risk. Table 4.3.2.1 provides a summary of the representative results from experimental toxicology studies with coumaphos for adult rats.

Table 4.3.2.1 – Coumaphos BMD_{10} Results (mg/kg/day) for RBC AChE Inhibition Over Time in Female and Male Adult Rats Following Oral Exposure		
Days of dosing	**RBC**	
	Males	**Females**
1 [a]	0.31	0.57
11 [b]	0.127	0.106
28 [e]	0.096	0.085
42 [c]	NT	0.08 [h]
57 [d]	0.16	0.17
90[d]	0.15	0.10
90 [e]	0.11	0.25
91 [f] **(F1)**	0.048	0.05
91 [g] **(F0)**	NRF	0.07

NRF = No Reliable Fit; NT= not tested;
[a] MRID 46258301 CCA Acute Study – Single Dose
[b] MRID 46502201 CCA Repeat Study – 11 days
[c] MRID 45912101 Developmental Neurotoxicity Study (i.e., gestational and lactational CCA data from lactation day 21); Results for maternal rats exposed 21 days during gestation and 21 days during lactation
[d] MRID 00126527 Subchronic Oral Study (lower doses than SCN and more inhibition at lower doses). Both 8 week and 13 week measures are available.
[e] MRID 44775901, subchronic neurotoxicity study; 4 week interim measures and 90 day final measures
[f] MRID 43061701 2 generation reproductive study; F1 generation.
[g] MRID 43061701 2 generation reproductive study; F0 generation based on visual inspection and taking into account the observed dose spacing issues this model fit is adequate and these data are reported for characterization purposes.
[h] p=0.03 model fit; based on visual inspection and taking into account the observed dose spacing issues this model fit is adequate and these data are reported for characterization purposes.

As shown in Table 4.3.2.1, the acute BMD values for adults are the highest in this table. With respect to BMD values from 11 days of dosing up to 90 days, there is remarkable similarity in the RBC BMD estimates across multiple studies (i.e., BMDs with a 3X range) in both sexes with the 2-generation reproduction study F0 and F1 generation rats providing the lowest values. In adults, OPs exhibit a phenomenon known as steady state cholinesterase (AChE) inhibition. After repeated dosing at the same level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks but this can vary among OPs. For coumaphos, the results in Table 4.3.2.1 show a clear pattern of steady state reached by 11 days of exposure. In addition to the consistency across durations, the data across multiple studies are similar. The data are also consistent with the OP cumulative risk assessment which included subchronic and chronic data for coumaphos.

Although the durations of the toxicity and exposure assessments may differ among the OPs, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and also provides consistency with the OP cumulative risk assessment (OP Cumulative Risk Assessment (CRA); 2002, 2006) and across the single chemical risk assessment for the OPs. As such, the single chemical OP assessment will evaluate steady state (a 21-day assessment) instead of the typical chronic duration dietary assessment. The steady state point of departure is protective of any exposure duration longer than 21-days, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady state.

Given the results in Table 4.3.2.1, for coumaphos, single day and steady state durations are appropriate for human health risk assessment. As such, the endpoint selection for coumaphos focuses on acute, single day effects, and steady state effects (21 days and longer).

4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the Agency has used inhibition of AChE as the PoD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PoDs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PoDs for coumaphos. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk assessment ((D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al., 12/29/2014). Initially, the agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[3]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years. For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/2015), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were

[3] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.-1; CDC, 2008)[4]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

Table 4.4-1. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorviphos	X					
Trichlorfon	X					

DMP = dimethylphosphate;DEP = diethylphosphate;DMTP = dimethylthiophosphate;DMDTP = dimethyldithiophosphate;DETP = diethylthiophosphate;DEDTP = diethyldithiophosphate.

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from

[4] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf

chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al., 2008; Chen et al., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al., 2008; Chen et al., 2012; Racke et al., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al., 2008; Forsberg et al., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations between for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, and CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and ADHD were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] investigators with additional support from a case control study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral

problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al. ,2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the PBPK-PD model (D424485, D. Drew et al., 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[5] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and

[5] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/2015). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b) (2) (C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for

neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the coumaphos PRA, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

4.5 Safety Factor for Infants and Children (FQPA Safety Factor)

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and critical window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety Factor will be retained for coumaphos for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios.**

Additionally, there is a data gap for coumaphos for a subchronic inhalation study. Therefore, a total database uncertainty factor of 30X, to account for the uncertainty in the human dose-response relationship for neurodevelopmental effects and the lack of an inhalation, will be used for coumaphos for the population subgroups that include infants, children, youth, and women of childbearing age for inhalation exposure scenarios.

4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for coumaphos is complete, with the exception of a subchronic inhalation study and a coumaphos oxon CCA study. Available studies include developmental studies in rat and rabbit, a reproductive toxicity study, a DNT, and a comparative ChE study with three components (acute, repeated, and gestational). A CCA study for the oxon is not available, and exposure to the oxon is considered to be 50X as toxic as exposure to the parent in the absence of this study (See Section 4.6.2 for details).

4.5.2 Evidence of Neurotoxicity

Coumaphos is an OP with a neurotoxic MOA/AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used in deriving PoDs for risk assessment.

4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Comparative AChE studies are available and provide quality AChE dose response data from potentially susceptible lifestages (i.e., fetuses, pregnant dams, post-natal pups). In the acute and repeat CCA rat studies juvenile animals were more sensitive than adults to both RBC and brain AChE inhibition at peak time of inhibition at high doses (i.e., > 1 mg/kg/day), but not at low doses near the PoDs for 10% RBC AChE inhibition. In addition, the gestational dosing CCA study does not show any lifestage sensitivity to coumaphos-induced AChE inhibition. Rat and rabbit developmental studies are also available that do not show any susceptibility (although they did not measure AChE inhibition). Similarly, the reproductive toxicity study and developmental neurotoxicity (DNT) study provide no evidence of quantitative lifestage susceptibility. In the 2-generation reproduction and DNT studies, the parental animals had more robust AChE inhibition than the offspring at similar doses; however, the parental animal measurements and BMD analysis have greater uncertainty and are only provided for characterization purposes. Qualitative susceptibility (morphometric brain changes in offspring) recorded in the DNT study was only observed at much higher doses (70 fold higher) than those selected for PoD derivation. Moreover, BMD results using RBC AChE inhibition are protective for the effects on the pups observed in the DNT and repeat CCA studies.

The acute and steady state PoDs are based on the most sensitive $BMDL_{10}$s for RBC AChE (the most sensitive compartment), and thus are protective of the observed sensitivity of juvenile rats.

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios.

4.5.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The partially refined dietary risk assessment uses anticipated residues from monitoring data, estimated drinking water concentrations from maximum application rate, and 100% crop treated and will not underestimate dietary (food and water) exposure to coumaphos. All of the exposure and risk estimates are based on conservative assumptions that do not underestimate risk. There are no registered residential uses for coumaphos.

4.6 Toxicity Endpoint and Point of Departure Selections

4.6.1 Dose-Response Assessment

Table 4.6.5.1 summarizes the coumaphos toxicity endpoints and PoDs selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: For coumaphos, across all studies, durations, lifestages, and routes, the RBC AChE is more sensitive than the brain compartment. As such, OPP has emphasized the RBC data in PoD derivation as these data tend to be less variable than brain data because of a lack of brain AChE inhibition in

many studies, and thus a majority of brain data were not suitable for BMD analysis, or had a poor dose response.

- *Potentially susceptible populations (fetuses, juveniles, pregnancy*): The available oral AChE data across multiple lifestages (adults, pregnant adults, fetuses, juveniles) show lifestage sensitivity for acute and repeat oral exposures at doses > 1 mg/kg/day, but not for gestational exposure. However, there is no sensitivity at low doses near the PoDs used for risk assessment (0.04-0.19 mg/kg/day). Based on the oral studies, lifestage sensitivity is not expected for dermal and inhalation routes of exposure.
- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. In the case of coumaphos, there are oral and dermal studies that contain quality dose response AChE data. The majority of oral studies are via dietary exposure.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with that of the exposure duration of interest. In the case of coumaphos, there are single day and repeated dosing oral studies, and 2-, 5-, and 21-day dermal studies are available.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent across studies. The coumaphos database demonstrates a striking consistency across studies which allows for PoDs to be derived from multiple critical studies, thereby, increasing the confidence in such values.

Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix 3. Summary tables of BMD analyses can be found in Appendix 2 and the technical details of the analysis can be found in the BMD memo (Liccione & Holman, 8/5/2014, TXR #0057001)

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10}s and $BMDL_{10}$s. The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the Agency uses the BMDL, not the BMD, for use as the PoD (USEPA, 2012). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.2; an exponential model was used to fit the data, with the assumption of constant variance across each dataset.

Acute Dietary (all populations)

As shown in Appendix Table 2.1, results of the single dosing CCA study with coumaphos are comparable for RBC AChE data in pups ages post-natal day (PND) 11 and adult male and female rats. A PoD for the acute dietary (all populations) exposure scenario was derived from the results of a well-conducted acute CCA rat study (MRID 46258301). A $BMDL_{10}$ of 0.19 mg/kg/day associated with RBC AChE inhibition in adult males was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding BMD_{10} was 0.31 mg/kg/day. This BMDL10 is protective of RBC AChE inhibition in PND11 pups, as the BMDL10 for pups is 0.25 mg/kg, and the PND 11 pups represent the most highly exposed sub-populations (infants and young children).

The acute neurotoxicity study was not selected because it did not measure AChE at the peak time of inhibition (4 hours for adults and 8 hours for pups). RBC AChE inhibition was selected for the PoD because it was more sensitive than brain AChE inhibition in pups, and the brain ChE data for adults did not provide a reliable fit in the benchmark dose analysis, due to the lack of a response.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/ database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an aPAD of 0.00019 mg/kg/day for exposure scenarios with infants, children, youth, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the aPAD for this population subgroup is 0.0019 mg/kg/day.

Steady-State Dietary (all populations)

Table 4.3.2.1 and Appendix Table 2.2 show remarkable similarity in RBC BMD estimates across multiple studies and durations for adults in studies 11 days and longer (i.e., BMDs within 3X range). A PoD for the steady state dietary (all populations) exposure scenario was derived from the results of a 2 generation reproduction study (MRID 43061701). A $BMDL_{10}$ of 0.04 mg/kg/day (0.036 mg/kg/day rounded) associated with RBC AChE inhibition in both male and female adult rats of the F0 and F1 generation was selected as a suitable PoD for the steady-state dietary (all populations) exposure scenario. The corresponding BMD_{10}s were 0.05/0.07 mg/kg/day in females and males, respectively.

This endpoint is considered appropriate for steady state dietary exposure due to the oral route of administration and the chronic duration of exposure. The study and endpoint were selected because they are protective of effects observed in all the other available studies for all lifestages, including offspring effects seen in the DNT study, and RBC AChE inhibition in the PND 11 pups of the repeat CCA study.

The PoD of 0.04 mg/kg/day for RBC AChE inhibition is supported by several other studies including:

- $BMDL_{10}$ of 0.041/0.042 mg/kg/day (males/females) in PND 11 pups in repeat CCA study via gavage (11 days) (MRID 46502201)
- $BMDL_{10}$ of 0.03 mg/kg/day in dams of the DNT study following gestational and lactation exposure via diet (42 days) (MRID 45912101)

The female data in the DNT study and F0 generation did not yield statistically acceptable results with a p-value of 0.05 using a log-likelihood ratio test. However, visual observation of the data shows a good fit and comparable findings to the F1 generation data, which were selected as the PoD.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/ database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain a ssPAD[6] of 0.00004 mg/kg/day for exposure scenarios with infants, children, youth, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the ssPAD for this population subgroup is 0.0004 mg/kg/day.

Dermal, Steady State

Based on the use pattern for coumaphos, only a repeated exposure dermal PoD is required. Therefore, the two available 21-day dermal studies were used for the steady state dermal assessment.

A steady state dermal PoD was selected from a 21-day dermal toxicity study (MRID 42666401) in rats based on RBC AChE inhibition ($BMDL_{10}$ = 0.5 mg/kg/day; BMD_{10} = 0.72 mg/kg/day) in the female rat. It is noted that the female and male data for the second dermal study (that tested higher doses of 2, 4, 20 and 100 mg/kg/day) did not provide statistically acceptable results with a p-value of 0.05 using a log-likelihood ratio test for RBC AChE inhibition; however, visual observation of the data show good fit and similar findings were obtained in females in this study ($BMDL_{10}$ of 0.71 mg/kg/day). RBC AChE inhibition was significantly more sensitive than brain AChE inhibition (between 6 and 8.3 fold) in the dermal toxicity study.

A total uncertainty factor of 1000X is appropriate for dermal exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments or a database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)), allowing a level of concern (LOC) of 1000X.

Inhalation, Steady State

Based on the use pattern for coumaphos, only a steady-state inhalation PoD is required to assess occupational exposure and risk. In the absence of a repeat dose inhalation study, an oral study was used. In addition, it was assumed that the time to reach steady state is comparable for oral and inhalation exposure.

A PoD for the steady state inhalation exposure scenario was derived from the results of a 2 generation reproduction study (MRID 43061701). A BMD_{10} of 0.05 mg/kg/day associated with RBC AChE inhibition in both male and female adult rats of the F0 and F1 generations from the 2 generation reproductive study was selected as a suitable PoD for the steady-state inhalation (all populations) exposure scenario. The corresponding $BMDL_{10}$ was 0.04 (0.036 rounded) mg/kg/day. Toxicity by the inhalation route was considered to be equivalent to toxicity by the oral route. However, in some cases toxicity via the inhalation route is higher than toxicity via the oral exposure, which results in an underestimation of risks from inhalation exposure. In addition, there may be a potential for portal of entry effects via the inhalation route, which would

[6] ssPAD: Population adjusted dose derived from steady state duration

not be accounted for in the oral studies. As a result, the HASPOC concluded that an inhalation study is needed for a more accurate assessment of inhalation risks.

The total uncertainty factor of 3000X was applied (10X for interspecies extrapolation, 10X for intraspecies variation, and 30X database uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4) and because there is an unfulfilled inhalation study requirement for coumaphos), allowing a LOC of 3000X.

4.6.2 Oxon Toxicity Adjustment Factor

In the 2006 updated OP cumulative risk assessment (CRA), the Agency characterized the potential impacts of the conversion of OP pesticides to oxon transformation products during standard drinking water treatment processes. For those OP pesticides that could potentially transform into more toxic oxons, the Agency assumed a complete transformation as a result of drinking water treatment. Based on limited data (documented in the 2002 OP CRA), the Agency assumed that the oxons would persist for a sufficient time to travel through the distribution system.

The Agency used submitted data to characterize the relative toxicity differences between the oxon and the parent for some of the OP pesticides; information from published literature was also available to inform relative potency for a few OP Pesticides[1]. For those OP pesticides without sufficient oxon data, the Agency initially used upper bound oxon adjustment factors of 10X and 100X for estimating potential oxon potency. The 100X was used considering the highest relative toxicity difference observed (61X) for malathion/maloxon, based on the data available at the time. However, since then, acute and repeat dose CCA studies have been submitted for both malathion and malaoxon. The new data allows a direct comparison of relative toxicity for the two chemicals and therefore, reduces uncertainty; an oxon adjustment factor of 22X was determined based on this data. As a result, a 50X oxon adjustment factor has been used for the OP draft risk assessments for registration review to estimate potential oxon potency. The 50X accounts for the highest oxon adjustment factor of 22X with an additional safety margin to protect for potential oxon toxicity for chemicals without oxon data. The adjustment factors were applied to residues for risk assessment of all exposure durations, routes, and scenarios.

[1] Chambers JE, Carr RL. 1993. "Inhibition patterns of brain acetylcholinesterase and hepatic and plasma aliesterases following exposures to three phosphorothionate insecticides and their oxons in rats." Fundamental and Applied Toxicology. Jul; 21(1):111_9.

OP PESTICIDE	OXON ADJUSTMENT FACTOR
Azinphos-Methyl	No data
Bensulide	No data
Chlorethoxyfos	No data
Chlorpyrifos	11.9X (acute); 18X (repeated): RBC
Coumaphos	No data
Diazinon	12.1X (acute); 9.0X (repeated):RBC
Dimethoate	8 X (acute); 3X (repeated): Brain
Disulfoton	No data
Malathion	22X (acute); 22X (repeated): RBC
+-Methidathion	No data
Methyl Parathion	<10X (Chambers and Carr, 1993)*
Phostebupirim	No data
Propetamphos	No data
Temephos	No data

Oxon toxicity adjustment factors are based on a comparison of the most sensitive compartment (i.e., RBC or brain) determined for the chemical.

4.6.3 Recommendations for Combining Routes of Exposures for Risk

PoDs for the oral, dermal, and inhalation routes are all derived from RBC AChE inhibition. Thus, all routes can be combined.

4.6.4 Cancer Classification and Risk Assessment Recommendation

There is no evidence of carcinogenicity in adequate studies in rats and mice and no evidence of mutagenicity. Therefore, coumaphos is classified as "not likely to be carcinogenic in humans."

4.6.5 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.6.5.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Coumaphos in Dietary Human Health Risk Assessments

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/ FQPA Factors[5]	RFD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 0.19 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	Acute RfD =0.0019 mg/kg aPAD = 0.00019 mg/kg	CCA Study (MRID 46258301) in the rat BMD10 = 0.31 mg/kg (adult males) for inhibition of RBC AChE in adult male rats.
Acute Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 0.19 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Acute RfD = 0.0019 mg/kg aPAD = 0.0019 mg/kg	CCA Study (MRID 46258301) in the rat BMD10 = 0.31 mg/kg (adult males) for inhibition of RBC AChE in adult male rats.
Steady-State Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 0.04 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	ssRfD = 0.0004 mg/kg ssPAD = 0.00004 mg/kg/day	2 generation reproductive study (MRID 43061701) BMD10 = 0.05 mg/kg/day for Inhibition of RBC AChE in in F0 and F1 young adults at 90 days in both males and females
Steady-State Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 0.04 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	ssRfD = 0.0004 mg/kg ssPAD = 0.0004 mg/kg/day	2 generation reproductive study (MRID 43061701) BMD10 = 0.05 mg/kg/day for Inhibition of RBC AChE in in F0 and F1 young adults at 90 days in both males and females
Cancer (oral, dermal, inhalation)	Classification: not likely to be carcinogenic in humans			

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. $BMDL_{10}$ = lower confidence interval on the benchmark dose for 10% response. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, ss = steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic). RfD = reference dose.

Table 4.6.5.2 Summary of Toxicological Doses and Endpoints for Coumaphos for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Steady State (21 days and longer)	$BMDL_{10}$ = 0.5 mg/kg/day	UF_A=10x UF_H=10x UF_{DB} = 10x[a]	Occupational LOC for MOE = 1000	21-day dermal toxicity study (MRID 42666401) in female rats BMD_{10} = 0.72 mg/kg/day for inhibition of RBC AChE in adult female rats.
Inhalation Steady State (21 days and longer)	$BMDL_{10}$ = 0.04 mg/kg/day Inhalation absorption 100% of oral absorption	UF_A=10x UF_H=10x UF_{DB}= 30x[b]	Occupational LOC for MOE = 3000	2 generation reproductive study (MRID 43061701) BMD_{10} = 0.05 mg/kg/day for Inhibition of RBC AChE in F_0 and F_1 young adults at 90 days in both males and females
Cancer (oral, dermal, inhalation)	Classification: not likely to be carcinogenic in humans			

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. $BMDL_{10}$ = lower confidence interval on the benchmark dose for 10% response. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = database uncertainty factor. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. Steady state = maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The steady state assessment is protective of longer durations including chronic.

[a] UF_{DB} for occupational dermal exposures = database uncertainty factor for uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

[b] UF_{DB} for occupational inhalation exposures = database uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4) and the UF_L due to lack of a NOAEL in the sub-chronic inhalation toxicity study.

4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for coumaphos, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), coumaphos is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a

chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[6] and includes some pesticides including coumaphos scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Coumaphos is on List 2. List 2 represents the next set of chemicals for which EPA intends to issue test orders/data call-ins in the near future. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[7].

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

No primary crop metabolism data are required, as coumaphos is not registered for use on plants. In honeybee products (honey and honeycomb), the residues of concern are coumaphos and its oxygen analog, coumaphoxon. The nature of the residue in ruminants has been established, based on an adequate ruminant metabolism study reflecting dermal dosing. In livestock, the residues of concern for risk assessment and for tolerance enforcement are coumaphos and coumaphoxon. The registrant has canceled uses on poultry; therefore, there is no requirement for poultry metabolism data.

5.1.2 Summary of Environmental Degradation

Coumaphos is persistent in the environment and slightly mobile to hardly mobile in soil. The major pathway of coumaphos degradation appears to be photodegradation in water. Results of the field dissipation study support the finding that coumaphos is persistent; however, coumaphos moved to greater depths than expected based on its K_d values. A major degradate, the oxygen analog, coumaphoxon, was detected in an aqueous photodegradation study at a maximum of 10.2% of applied chemical. Limited environmental fate data are available for coumaphoxon, which suggests that it is not persistent in the terrestrial environment, but it is mobile in soil. Coumaphos accounted for 0.4% of leachate from a sandy loam column and less than 2% of leachate from columns of sand, silt loam, and silty clay loam.

5.1.3 Comparison of Metabolite Pathways

There are no direct uses of coumaphos on plants; therefore, a discussion of comparative metabolic pathways is not pertinent to this assessment. Coumaphos, like some other OPs, requires metabolic activation to the oxon metabolite to inhibit AChE, with subsequent metabolism that leads to detoxification. Coumaphos is metabolized in animals by oxidation to its hydrolysis product chlorferon (dephosphorylated coumaphos). Following oral administration in the rat metabolism study, coumaphos was rapidly absorbed and eliminated in urine and feces with no evidence of bioaccumulation and the major metabolite is chlorferon (See Section 4.2).

5.1.4 Residues of Concern Summary and Rationale

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Not Applicable [1]	Not Applicable[1]
	Rotational Crop	Not Applicable[1]	Not Applicable[1]
Livestock	Ruminant	Parent and oxygen analog (coumaphoxon)	Parent and oxygen analog (coumaphoxon)
	Poultry	Not Applicable [2]	Not Applicable [2]
Drinking Water		Parent and oxygen analog (coumaphoxon)	Parent and oxygen analog (coumaphoxon)

[1] There are currently no registered uses of coumaphos on plants. Honey and beeswax (honeycomb) residue of concern are coumaphos and its oxygen analog coumaphoxon (coumaphos-PO).
[2] There are currently no registered uses of coumaphos on poultry.

5.2 Food Residue Profile

Coumaphos is an insecticide used to control arthropod pests on livestock and used in beehives (impregnated strips) for the control of mites and small hive beetles. Plant metabolism data are not available for coumaphos. Based on the ruminant metabolism study, coumaphos was the major residue accounting for 70-96% of the residue in tissues and its metabolite, coumaphoxon was not detected in the muscle or fat. Accumulation of coumaphos residues in honey and beeswax following treatment of hives with coumaphos-impregnated strips were shown to be considerably higher in beeswax than in honey. Field trial data looked for the parent and coumaphoxon in honey/beeswax and found no detectable resides of coumaphoxon. Magnitude of residue studies reflecting the current types of registered external uses (dusts, sprays, dips, pour-ons, backrubbers, and bedding treatments) and feeding studies were reviewed. The feeding study looked for the combined residue of parent and coumaphoxon in livestock and found detectable residues in livestock tissues (primarily fat samples). However, PDP monitoring data for honey and livestock commodities looked for the parent separately from the oxon and found detectable parent residues, but no coumaphoxon. Therefore, coumaphoxon is not expected to be found in food and a TAF of 50x was not used for food and was only applied to drinking water.

5.3 Water Residue Profile

Coumaphos indoor use (e.g. to treat swine bedding) and the placement of coumaphos-treated strips in bee hives were not considered in the drinking water assessment because they do not provide complete routes of exposure to surface water or groundwater. However, during a rain event, a certain fraction of coumaphos wash-off from treated cattle can come into contact with and be adsorbed onto manure as well as transported as runoff from concentrated animal feeding operations and pasture/rangeland.

The estimated drinking water concentration (EDWCs) of coumaphos and coumaphoxon were generated using the Tier II Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) model for surface water and Tier I SCIGROW (Screening Concentration in Ground Water Program) for groundwater. Pesticide Root Zone Model-Ground Water model (PRZM-GW) was also used for ground water. The drinking water assessment assumed that during a rain event, coumaphos wash-off from treated cattle can be potentially adsorbed into manure as well as transported as effluent from concentrated animal feeding operations and pasture/rangeland. Use of this product is restricted to employees of the USDA-APHIS[7] who are enrolled in the USDA-APHIS cholinesterase monitoring program. The USDA's Cattle Fever Tick Eradication Program (CFTEP) uses this product solely in Texas. As a result, the TX Barton Springs Segment of the Edward Aquifer scenario with a 2% wash-off fraction after 24 hours dip-vat treatment in the leaching study was used.

The residues of concern for drinking water are coumaphos and its oxygen analog, coumaphoxon. A maximum conversion efficiency of coumaphos to coumaphoxon of 10.2% was derived from available data on photodegradation in water. This conversion efficiency was used to estimate a coumaphoxon application rate of 0.0285 lbs ai/A for drinking water modeling. However, a more conservative estimate is to assume 100% conversion to oxygen analog if it was determined that oxygen analog is more toxic than its parent. Coumaphos exposed to chlorine in drinking water treatment facilities is expected to be rapidly and completely converted to coumaphoxon and is multiplied by the TAF of 50X to take into account conversion to coumaphoxon. Final time series provided to HED are multiplied by 1.05 to convert from coumaphos (362.76 g/mol) to coumaphoxon (346.7 g/mol).

Table 5.3 summarizes recommended EDWCs for surface water and groundwater. However, for acute and steady state assessments, the entire 30-year distribution of estimated daily concentrations was incorporated into the PRZM/EXAMS and used in the probabilistic analyses. For steady state, the TX scenario daily time series was also recalculated using the 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc.

[7] APHIS- Animal and Plant Health Inspection Service

Table 5.3. Maximum EDWCs for Drinking Water Sources for Coumaphos and Coumaphoxon			
Source of Drinking Water	Estimated Drinking Water concentration (µg/L)		
	Acute	Chronic	Average chronic
Coumaphos			
Surface Water[1]	0.10	0.05	0.03
Groundwater[2]	1.91×10^{-03}	1.91×10^{-03}	1.91×10^{-03}
Coumaphoxon			
Surface Water	0.002	0.0001	6.89×10^{-05}
Groundwater[2]	5.06×10^{-06}	5.06×10^{-06}	5.06×10^{-06}
Coumaphos Equivalents (Coumaphos+Coumaphoxon)[3]			
Surface Water	0.102	0.05	0.03
Groundwater	1.92×10^{-03}	1.92×10^{-03}	1.92×10^{-03}

[1] EDWCs based on PRZM/EXAMS model
[2] EDWCs derived from SCIGROW
[3] Coumaphos + Coumaphoxon- sum of surface water/and or groundwater for coumaphos and coumaphoxon, respectively

5.4 Dietary Risk Assessment

Reference: D412870; S. Piper, February 4, 2016

5.4.1 Description of Residue Data Used in Dietary Assessment

Partially refined acute and steady state dietary exposure and risk assessments for coumaphos were conducted using DEEM-FCID version 3.18. This model uses 2003-2008 food consumption data from USDA's National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). The dietary exposure assessments incorporated USDA Pesticide Data Program (PDP) monitoring data for coumaphos and its metabolite (coumaphoxon) in/on honey, milk, and livestock commodities and assumed 100% crop treated. The dietary exposure assessment assumes a 50x TAF for coumaphoxon in drinking water, DEEM default processing factors, and100% CT. Acute and steady-state assessments were conducted for food only, drinking water only, and food and drinking water.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The dietary exposure assessment assumes 100% crop treated for honey for the acute and steady state dietary exposure assessments. BEAD has no information on honey *(per* conversation with D. Atwood and S. Smearman).

5.4.3 Acute Dietary Risk Assessment

The acute dietary exposure estimates are summarized in Tables 5.4.3.1-5.4.3.3 and are below HED's LOC (<100% of the aPAD) for the U.S. population and all population subgroups at the 99.9th percentile. The food only dietary exposure estimate is 50% of the acute population adjusted dose (aPAD) for the U.S. population, and 98% of the aPAD for children 3-5 years old, the most highly exposed population subgroup at the 99.9th percentile. Combined dietary exposure from food and drinking water at the 99.9th percentile of exposure is 51% of the aPAD for the U.S. population and 99% of the aPAD for children 3-5 years, the most highly exposed

population subgroup. The drinking water only dietary exposure estimate is 7% of the aPAD for the U.S. population, and 20% of the aPAD for all infants (<1 years old), the most highly-exposed population subgroup, at the 99.9th percentile. Beef meat is the risk driver when combining food in the acute assessment for coumaphos, accounting for approximately 80% of estimated exposure in the acute assessment based upon critical exposure contribution analysis.

Table 5.4.3.1. Summary of Acute Dietary (Food Only) Exposure and Risk for Coumaphos

Population Subgroup	aPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD
General U.S. Population	0.00019	0.000029	16	0.000051	27	0.000096	50
All Infants (<1 year old)	0.00019	0.000034	18	0.000068	36	0.000158	83
Children 1-2 years old	0.00019	0.000061	32	0.000100	52	0.000168	88
Children 3-5 years old	0.00019	0.000054	29	0.000095	50	**0.000187**	**98**
Children 6-12 years old	0.00019	0.000039	21	0.000064	34	0.000106	56
Youth 13-19 years old	0.00019	0.000028	15	0.000045	24	0.000082	43
Adults 20-49 years old	0.00019	0.000026	13	0.000041	21	0.000066	34
Adults 50-99 years old	0.0019	0.000020	1.0	0.000033	1.8	0.000051	2.7
Females 13-49 years old	0.00019	0.000022	11	0.000036	19	0.000060	32

mkd = mg/kg/day. aPAD= acute population adjusted dose; Highest exposure at the 99.9th percentile is in bold font.

Table 5.4.3.2. Summary of Acute Dietary (Drinking Water Only) Exposure and Risk for Coumaphos

Population Subgroup	aPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD
General U.S. Population	0.00019	0.000002	1.2	0.00004	2.3	0.000014	7.3
All Infants (<1 year old)	0.00019	**0.000007**	**3.6**	**0.000011**	**6.1**	**0.000037**	**20**
Children 1-2 years old	0.00019	0.000003	1.8	0.000006	3.4	0.000020	11
Children 3-5 years old	0.00019	0.000003	1.5	0.000005	2.6	0.000018	9.5
Children 6-12 years old	0.00019	0.000002	1.1	0.000004	2.1	0.000012	6.5
Youth 13-19 years old	0.00019	0.000002	<1	0.000003	1.8	0.000010	5.2
Adults 20-49 years old	0.00019	0.000002	1.2	0.000004	2.0	0.000013	7.0
Adults 50-99 years old	0.0019	0.000002	<1	0.000004	<1	0.000013	<1
Females 13-49 years old	0.00019	0.000002	1.2	0.000004	2.1	0.000013	7.0

mkd = mg/kg/day. aPAD= acute population adjusted dose; Highest exposure at the 99.9th percentile is in bold font.

Table 5.4.3.3. Summary of Acute Dietary (Food and TX Drinking Water) Exposure and Risk for Coumaphos

Population Subgroup	aPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD
General U.S. Population	0.00019	0.000030	16	0.000052	27	0.000098	51
All Infants (<1 year old)	0.00019	0.000035	19	0.000070	37	0.000161	85
Children 1-2 years old	0.00019	0.000062	32	0.000100	53	0.000171	90
Children 3-5 years old	0.00019	0.000056	29	0.000096	51	**0.000188**	**99**
Children 6-12 years old	0.00019	0.000040	21	0.000065	34	0.000107	56
Youth 13-19 years old	0.00019	0.000029	15	0.000045	24	0.000083	44
Adults 20-49 years old	0.00019	0.000026	14	0.000041	22	0.000067	35
Adults 50-99 years old	0.0019	0.000021	1.1	0.000035	1.8	0.000055	2.9

Table 5.4.3.3. Summary of Acute Dietary (Food and TX Drinking Water) Exposure and Risk for Coumaphos							
Population Subgroup	aPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD
Females 13-49 years old	0.00019	0.000023	12	0.000038	20	0.000064	34

mkd = mg/kg/day. aPAD= acute population adjusted dose; Highest exposure at the 99.9th percentile is in bold font.

5.4.4 Steady State Dietary Risk Assessment

Steady-state assessments were conducted in the DEEM acute module using the steady-state endpoint, PDP monitoring residue distributions and 21-day rolling water averages to provide an estimate of 21-day ("steady-state") exposures. Steady-state assessments were conducted for drinking water alone, food alone, and food + drinking water.

As shown in Tables 5.4.4.1-5.4.4.3 the steady state aggregate dietary (food alone, water alone and food plus drinking water) exposure estimates are above HED's LOC (>100% of the PAD) for the U.S. population and all population subgroups, except adults 50-99 years old. The food only dietary exposure estimate is 210% of ssPAD for the U.S. population, and 380% of the ssPAD for children 1-2 years old, the most highly exposed population subgroup at the 99.9th percentile. The drinking water only dietary exposure estimate is 36% of the ssPAD for the U.S. population and 110% of the ssPAD for all infants (<1 year old), the most highly-exposed population subgroup, at the 99.9th percentile. Combined dietary exposure from food and drinking water is 210% of the ssPAD for the U.S. population and 390% of the ssPAD for children 1-2 years, the most highly exposed population subgroup. Beef meat is the risk driver when combining food in the steady state assessment for coumaphos, accounting for approximately 90% of estimated exposure in the acute assessment based upon critical exposure contribution analysis.

Table 5.4.4.1. Summary of Steady State Dietary (Food Only) Exposure and Risk for Coumaphos							
Population Subgroup	ssPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD
General U.S. Population	0.00004	0.000023	64	0.000037	100	0.000074	210
All Infants (<1 year old)	0.00004	0.000027	76	0.000050	140	0.000117	330
Children 1-2 years old	0.00004	0.000044	120	0.000066	180	**0.000137**	**380**
Children 3-5 years old	0.00004	0.000043	120	0.000073	200	0.000112	310
Children 6-12 years old	0.00004	0.000031	87	0.000045	130	0.000097	270
Youth 13-19 years old	0.00004	0.000022	62	0.000032	90	0.000054	150
Adults 20-49 years old	0.00004	0.000021	57	0.000030	84	0.000049	140
Adults 50-99 years old	0.0004	0.000016	4.6	0.000025	6.8	0.000034	9.4
Females 13-49 years old	0.00004	0.000018	49	0.000026	72	0.000049	140

mkd = mg/kg/day. ssPAD= steady state population adjusted dose; Highest exposure at the 99.9th percentile is in bold font

Table 5.4.4.2. Summary of Steady State Dietary (Drinking Water Only) Exposure and Risk for Coumaphos							
Population Subgroup	ssPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD
General U.S. Population	0.00004	0.000007	5.9	0.00004	11	0.000013	36
All Infants (<1 year old)	0.00004	**0.000003**	**18**	**0.000011**	**30**	**0.000039**	**110**
Children 1-2 years old	0.00004	0.000003	8.8	0.000006	16	0.000018	51
Children 3-5 years old	0.00004	0.000003	7.1	0.000005	13	0.000015	42
Children 6-12 years old	0.00004	0.000002	5.3	0.000003	9.7	0.000011	31
Youth 13-19 years old	0.00004	0.000002	4.7	0.000003	8.2	0.000009	26
Adults 20-49 years old	0.00004	0.000002	5.7	0.000004	9.9	0.000013	35
Adults 50-99 years old	0.0004	0.000002	<1	0.000003	<1	0.000012	3.4
Females 13-49 years old	0.00004	0.000002	5.9	0.000004	9.8	0.000013	35

mkd = mg/kg/day. ssPAD= steady state population adjusted dose; Highest exposure at the 99.9th percentile is in bold font

Table 5.4.4.3. Summary of Steady State Dietary (Food and TX Drinking Water) Exposure and Risk for Coumaphos							
Population Subgroup	ssPAD (mkd)	95th Percentile		99th Percentile		**99.9th Percentile**	
		Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD
General U.S. Population	0.00004	0.000024	67	0.000039	110	0.000075	210
All Infants (<1 year old)	0.00004	0.000029	81	0.000056	150	0.000123	340
Children 1-2 years old	0.00004	0.000046	130	0.000067	190	**0.000140**	**390**
Children 3-5 years old	0.00004	0.000044	120	0.000074	210	0.000114	320
Children 6-12 years old	0.00004	0.000032	89	0.000046	130	0.000098	270
Youth 13-19 years old	0.00004	0.000023	64	0.000033	91	0.000055	150
Adults 20-49 years old	0.00004	0.000021	59	0.000031	87	0.000051	140
Adults 50-99 years old	0.0004	0.000017	4.8	0.000026	7.1	0.000036	10
Females 13-49 years old	0.00004	0.000018	51	0.000028	77	0.000051	140

mkd = mg/kg/day. ssPAD= steady state population adjusted dose; Highest exposure at the 99.9th percentile is in bold font

5.4.5 Cancer Dietary Risk Assessment

Coumaphos is classified as "no evidence" of carcinogenicity for humans. Therefore, a cancer dietary exposure analysis is not required.

6.0 Residential and Other Non-Occupational Exposure and Risk Estimates

There are currently no registered non-occupational (residential) uses for coumaphos at this time.

6.1 Residential Risk Estimates for Use in Aggregate Assessment

There are no currently registered residential (non-occupational) uses of coumaphos. Based on the labeled use pattern and the exposure profile of coumaphos, there is no recommended residential contribution to the aggregate risk assessment.

6.2 Non Occupational Spray Drift Exposures and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast). The approach is outlined in the revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift. Coumaphos is not applied nor registered on use sites that are likely to result in spray drift. Therefore, a spray drift analysis is not included in this assessment.

6.3 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for coumaphos.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from dietary and residential sources are added together and compared to quantitative estimates of hazard (*e.g.*,

a NOAEL), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Because there are no residential uses for coumaphos at this time, the aggregate assessments include dietary exposures only.

7.1 Acute Aggregate Risk

The acute exposure estimates provided in the Dietary Exposure Section represent the acute aggregate exposure. See Section 5.4.3. The acute aggregate risks associated with the registered uses of coumaphos do not exceed HED's level of concern for the general U.S. population or any population subgroup.

7.2 Steady State Aggregate Risk

Because there are no residential uses for coumaphos, the aggregate assessments include dietary (food and water) exposures only. See Section 5.4.4. The steady state aggregate risks associated with the registered uses of coumaphos do exceed HED's level of concern for the general U.S. population or any population subgroup.

7.3 Cancer Aggregate Risk

Coumaphos has been classified as "Not likely to be Carcinogenic to Humans"; therefore, a cancer aggregate risk assessment is not required.

8.0 Cumulative Risk Characterization/Assessment

OPs, like coumaphos, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PoDs for each OP, including terbufos. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.5, OPP has retained the FQPA Safety Factor for OPs, including coumaphos, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes. The agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to the release of the

revised PRA. During this period, the agency will determine whether or not it is appropriate to apply the draft guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* for the neurodevelopment outcomes.

9.0 Occupational Exposure/Risk Characterization

Reference: D409347, D410244; B. Bobowiec, November 11, 2015

9.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational dermal and inhalation handler exposure is expected from the proposed uses. Applying ear tags to cattle and inserting pest control strips into bee hives was not quantitatively assessed. The exposure to these tasks was considered negligible based on the product formulation and glove requirement. Therefore, the quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- mixing/loading flowable concentrate for hydraulic type dip vats,
- mixing/loading flowable concentrate for swim type dip vats,
- mixing/loading flowable and emulsifiable concentrate for back rubber/oilers,
- loading dust into bags,
- applying dust with a shaker can to cattle, horses,
- applying dust to swine bedding via shaker can,
- mixing/loading/applying liquid sprays for backpack application,
- mixing/loading/applying liquid sprays for mechanically pressurized handguns, and
- mixing/loading/applying liquid sprays for manually pressurized hand-wands.

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. These are outlined in more detail in (B. Bobowiec, 20-March-2016, D409347, and D410244), but are summarized briefly below.

- *Application Rate*: Summary of the registered coumaphos products are outlined in the previous Table 3.3. In addition maximum application rates are presented in Tables 9.1.1 - 9.1.9 organized by registration number.
- *Unit Exposures:* scenario/equipment/formulation-specific exposure factors known as "unit exposures" as well as their corresponding estimates for area treated or amount of

solution handled are from HED's ExpoSAC Policy #9.1 or standard assumptions for livestock treatment.

- *Body Weight:* A female-specific body weight of 69 kg was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects. See section 4.4 for more information.
- *Absorption factors:* A dermal toxicity study is the basis of dermal points of departure, a dermal absorption factor is not required. The inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure.
- *Area Treated or Amount Handled:* There are label restrictions that Applicators are restricted to spraying no more than 100 animals in one day at the maximum application rate with handheld equipment and 200 animals a day at one half the maximum application rate. Dust applications to livestock via a shaker can is restricted to 25 animals a day and 1000 ft^2 of bedding a day. The amount treated or amount handled was based on guidance in HED ExpoSAC Policy 9.1, language restrictions on the labels, and HED's best professional judgement of tank and cattle herd sizes, as well as the previous assessment memo (D267778, R. Sandvig, August 3, 1999). Amount handled is summarized below.

    - Swim dip vats are estimated to hold 4,000 gallons of solution.
    - Hydraulic-type dip vats are estimated to hold 1,800 gallons of solution.
    - Back oil rubbers are estimated to hold 14 gallons of solution.
    - Livestock herd sizes were estimated as small (100 cows), medium (350 cows), and large (500 cows).
    - Mechanically pressurized handguns are estimated to hold 1,000 gallons of spray; however, using the language from the labels this amount was lowered to 400 and 100 gallons of spray a day.
    - Manually pressurized handwand and backpack application were assumed 40 gallons of spray a day.

HED typically classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. The endpoint selection for organophosphate pesticides including coumaphos involves a "steady state" approach based on an individual chemical's cholinesterase inhibition. The "steady state" endpoint selection for coumaphos overlaps HED's traditional short-term endpoint selection as well as being appropriately health protective for occupational handlers that apply commercially over longer periods of time (i.e., intermediate-term exposures). Coumaphos can be toxic to livestock if over applied so it is assumed most farmers will only apply when pests are an issue. However, there is no quantitative data such as number of cattle dipped per day, number of days dipping takes place per year, etc. HED continues to request more quantitative data, such as the number of cattle dipped per day, number of days dipping takes place per year, etc., to refine exposure to dip vat workers in quarantine areas under the animal and plant health inspection service, (APHIS) USDA program.

Product labels vary with respect to work attire and levels of personal protective equipment, with some labels not providing any specifications to others requiring use of chemical/water-resistant gloves or respirators. Estimates of dermal and inhalation exposure were calculated for various levels degrees of mitigation. Results are presented for "baseline," defined as a single layer of

clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). Co-Ral Flowable, EPA Reg. No. 11556-98 has the highest spray application rates and requires handlers to wear a PF10 respirator. EPA Reg. Nos.11556-115 and 11556-23 have lower spray application rates and do not require any respirators for handlers. The various dust formulations require baseline dermal attire along with gloves and PF5 respirator. Protective eyewear, shield, and apron are also listed on some of the labels. See Section 4.6.4 for acute toxicity coumaphos summary. HED does not consider a face shield equivalent to a respirator nor an apron over long sleeve shirt equivalent to double layer protection.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix C. The toxicological PoDs for inputs can be found in the Section 4.6.4. A total aggregated risk index (ARI) approach was used since the toxicological effects for the dermal and inhalation exposure routes were similar (RBC cholinesterase inhibition), but the LOC values for dermal exposure (1000) and inhalation exposure (3000) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Based on the labeled PPE for occupational handlers for the various formulations, there are risk estimates of concern identified (i.e., dermal MOEs < 1000 and inhalation MOEs < 3000) for the steady-state exposure assessment. Combined occupational handler risk estimates are presented using the ARI approach with a target of 1.

There are dermal and inhalation risk estimates of concern for all formulation types and exposure scenarios except for back oil rubber applications. The products are sorted by formulation type (e.g., flowable, emulsifiable concentrate, and dust) with corresponding registration numbers. Risk estimates are presented in Tables 9.1.1. –9.1.9 with the unit exposures for each formulation presented in a separate tables. The unit formulation tables are then followed by scenario specific inhalation and dermal exposure risk estimates and then lastly followed by the ARI estimate tables. The following list provides a summary of the scenarios that resulted in risk estimates of concern:

- The USDA cholinesterase monitoring program scenarios include gloves and PF10 respirator and result in ARIs < 1. At label level PPE ARIs range from 0.003 to 0.06. ARIs range from 0.006 to 0.08 with PPE increased to double layer dermal protection and a PF10 respirator.
- The liquid coumaphos products that require gloves but no respirator also result in risk estimates of concern. At label level of PPE ARIs range from 0.002 to 0.7. ARIs range from 0.03 to 1.1 with PPE increased to double layer dermal protection and a PF10 respirator.
- The dust formulations require gloves and at least a PF5 respirator and result in result in ARIs < 1. At label level PPE ARIs range from 0.003 to 0.28. ARIs range from 0.006 to 0.46 with PPE increased to double layer dermal protection and a PF10 respirator.

Table 9.1.1. Dermal and Inhalation Unit Exposures for Dry Flowable Co-Ral Flowable Insecticide, REG # 11556-98

Application Equipment	Application Rate[2]	Amount Handled / Area Treated[3]	Dermal Unit Exposures (ug/lb ai)[1]				Inhalation Unit Exposures (ug/lb ai)[1]			
			SL/No G	SL/G	DL/G	EC	No-R	PF5 R	PF10 R	EC
Mixer/Loader										
Swim Dip Vat	0.025 lb ai/gallon of dip	4000 gallons/day	220	37.6	29.1	8.6	0.219	0.0438	0.0219	0.083
Hydraulic Dip Vat	0.025 lb ai/gallon of dip	1800 gallons/day	220	37.6	29.1	8.6	0.219	0.0438	0.0219	0.083
Mixer/Loader/Applicator										
Backpack	0.021 lb ai/gallon	40 gallons	2510	2500	1600	ND	30	6	3	ND
Manually-pressurized Handwand	0.021 lb ai/gallon	40 gallons	100000	430	365	ND	30	6	3	ND
Mechanically-pressurized Handgun	0.021 lb ai/gallon	100 gallons	1800	640	365	ND	79	15.8	7.9	ND
Mechanically-pressurized Handgun	0.021 lb ai/gallon	400 gallons	1800	640	365	ND	79	15.8	7.9	ND

1. Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015). PPE represented includes SL= baseline dermal (long sleeved shirt, long pants, shoes and socks), SL/G baseline dermal plus gloves, DL/G= coverall over baseline dermal plus gloves, EC= closed system. NR = no respirator; PF5 = "Protection Factor 5", indicating a reduction in exposure of 80%; PF10 = "Protection Factor 10" indicating a reduction in exposure of 90%.
2. Based on registered label Co-Ral Flowable Insecticide Reg # 11556-98. Label is restricted use to employees enrolled in the USDA-APHIS cholinesterase monitoring program.
3. Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1999 and EXPOSAC discussion 03/14/2013.

Table 9.1.2. Steady State-Term Duration Occupational Dermal and Inhalation Handler Non-Cancer Exposure and Risk Estimates for Co-Ral Flowable Insecticide, REG # 11556-98

Application Equipment	Application Rate[1]	Amount Handled / Area Treated[2]	Dermal Dose (mg/kg/day)[3]				Dermal MOE[4] (LOC=1000)				Inhalation Dose (mg/kg-day)[5]				Inhalation MOE[6] (LOC=3000)			
			SL/No G	SL/G	DL/G	EC	SL/No G	SL/G	DL/G	EC	No-R	PF5 R	PF10 R	EC	No-R	PF5 R	PF10 R	EC
Mixer/Loader																		
Swim Dip Vat	0.025 lb ai/gallon of dip	4000 gallons	0.319	0.055	0.042	0.013	1.6	9.2	12	40	0.0003	6.35E-05	3.17E-05	0.00012	110	570	1100	300
Hydraulic Dip Vat	0.025 lb ai/gallon of dip	1800 gallons	0.143	0.025	0.019	0.006	3.5	20	26	89	0.0001	2.86E-05	1.43E-05	5.42E-05	250	1300	2500	660
Mixer/Loader/Applicator																		
Backpack	0.021 lb ai/gallon	40 gallons	0.031	0.030	0.019	ND	16	16	26	ND	0.0004	7.3E-05	3.65E-05	ND	99	490	990	ND
Manually-pressurized Handwand	0.021 lb ai/gallon	40 gallons	1.22	0.005	0.004	ND	0.41	96	110	ND	0.0004	7.3E-05	3.65E-05	ND	99	490	990	ND
Mechanically-pressurized Handgun	0.021 lb ai/gallon	100 gallons	0.055	0.019	0.011	ND	9.1	26	45	ND	0.002	4.8E-04	2E-04	ND	15	75	150	ND
Mechanically-pressurized Handgun	0.021 lb ai/gallon	400 gallons	0.219	0.078	0.045	ND	2.3	6.4	11	ND	0.01	0.002	0.001	ND	3.7	19	37	ND

1 Based on registered label Co-Ral Flowable Insecticide Reg # 11556-98. Label is restricted use to employees enrolled in the USDA-APHIS cholinesterase monitoring program.
2 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1999 and EXPOSAC discussion 03/14/2013
3 Dermal Dose= Dermal Unit Exposure (µg/lbs a.i.) × Application Rate (lbs a.i./acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (69 kg).
4 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day)
5 Inhalation Dose = Inhalation Unit Exposure (µg/lbs a.i.) × Conversion Factor (0.001 mg/µg) × Application Rate (lbs a.i./acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (69 kg).
6 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table 9.1.3. Steady State-Term Duration Occupational ARI Handler Non-Cancer Exposure and Risk Estimates for Co-Ral Flowable Insecticide, REG # 11556-98[1]

Application Equipment	Application Rate[2]	Amount Handled / Area Treated[3]	ARI[4]							
			SL/No G + No-R	SL/G + No-R	DL/G + No-R	SL/G + PF5 R	DL/G + PF5 R	SL/G + PF10 R	DL/G + PF10 R	EC
Mixer/Loader										
Swim Dip Vat	0.025 lb ai/gallon of dip	4000 gallons	0.0015	0.0074	0.009	0.0088	0.011	0.009	0.012	0.029
Hydraulic Dip Vat	0.025 lb ai/gallon of dip	1800 gallons	0.0034	0.016	0.02	0.019	0.025	0.02	0.025	0.063
Mixer/Loader/Applicator										
Backpack	0.021 lb ai/gallon	40 gallons	0.011	0.011	0.015	0.015	0.022	0.015	0.024	ND
Manually-pressurized Handwand	0.021 lb ai/gallon	40 gallons	0.0004	0.025	0.025	0.06	0.066	0.074	0.083	ND
Mechanically-pressurized Handgun	0.021 lb ai/gallon	100 gallons	0.0032	0.0042	0.0045	0.013	0.016	0.017	0.024	ND
Mechanically-pressurized Handgun	0.021 lb ai/gallon	400 gallons	0.0008	0.001	0.0011	0.0032	0.004	0.0042	0.0058	ND

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015). Level of mitigation represented in table include: SL= baseline dermal (long sleeved shirt, long pants, shoes and socks), SL/G baseline dermal plus gloves, DL/G= coverall over baseline dermal plus gloves, EC= closed system. NR = no respirator; PF5 = "Protection Factor 5", indicating a reduction in exposure of 80%; PF10 = "Protection Factor 10" indicating a reduction in exposure of 90%.

2 Based on registered label Co-Ral Flowable Insecticide Reg # 11556-98. Label is restricted use to employees enrolled in the USDA-APHIS cholinesterase monitoring program

3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1999 and EXPOSAC discussion 03/14/2013

4 ARI = Aggregate Risk Index = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)].

Table 9.1.4 Steady State-Term Duration Unit Exposures for Liquid Formulations (Reg #s. 11556-115, and 11556-23)

Application Equipment	Target Animal	Application Rate[2]	Amount Handled / Area Treated[3]	Dermal Unit Exposures (ug/lb ai)[1]				Inhalation Unit Exposures (ug/lb ai)[1]			
				SL/No G	SL/G	DL/G	EC	No-R	PF5 R	PF10 R	EC
Mixer/Loader											
Back Oil Rubbers	Cattle	0.07617 lb ai/ gallon	14 gallons/day	220	37.6	29.1	8.6	0.219	0.0438	0.0219	0.083
Mixer/Loader/Applicator											
Backpack	Cattle	0.01 lb ai/gallon	40 gallons	2510	2500	1600	ND	30	6	3	ND
Backpack	Swine	0.005 lb ai/gallon									
Manually-pressurized Handwand	Cattle	0.01 lb ai/gallon	40 gallons	100000	430	365	ND	30	6	3	ND
Manually-pressurized Handwand	Swine	0.005 lb ai/gallon									
Mechanically-pressurized Handgun	Cattle	0.01 lb ai/gallon	100 gallons	1800	640	365	ND	79	15.8	7.9	ND
Mechanically-pressurized Handgun	Swine	0.005 lb ai/gallon	100 gallons	1800	640	365	ND	79	15.8	7.9	ND
Mechanically-pressurized Handgun	Cattle	0.01 lb ai/gallon	400 gallons	1800	640	365	ND	79	15.8	7.9	ND
Mechanically-pressurized Handgun	Swine	0.005 lb ai/gallon	400 gallons	1800	640	365	ND	79	15.8	7.9	ND

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015). PPE represented includes SL= baseline dermal (long sleeved shirt, long pants, shoes and socks), SL/G baseline dermal plus gloves, DL/G= coverall over baseline dermal plus gloves, EC= closed system. NR = no respirator; PF5 = "Protection Factor 5", indicating a reduction in exposure of 80%; PF10 = "Protection Factor 10" indicating a reduction in exposure of 90%.

2 Based on registered label Co-Ral Flowable Insecticide Reg # 11556-98. Label is restricted use to employees enrolled in the USDA-APHIS cholinesterase monitoring program

3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1999 and EXPOSAC discussion 03/14/2013.

Table 9.1.5. Steady State-Term Duration Occupational Handler Non-Cancer Exposure and Risk Estimates for Liquid Formulations (Reg #s. 11556-115, and 11556-23[1])

Application Equipment	Target Animal	Application Rate[2]	Amount Handled / Area Treated[3]	Dermal Dose (mg/kg/day)[4]				Dermal MOE[5] (LOC=1000)				Inhalation Dose (mg/kg-day)[6]				Inhalation MOE[7] (LOC=3000)			
				SL/ No G	SL/G	DL/G	EC	SL/ No G	SL/ G	DL/ G	EC	No-R	PF5 R	PF10 R	EC	No-R	PF5 R	PF10 R	EC
Mixer/Loader																			
Back Oil Rubbers	Cattle	0.07617 lb ai/ gallon	14 gallons/ day	0.003	0.001	0.0005	0.0001	150	860	1100	3800	3.39E-06	6.77E-07	3.39E-07	1.28E-06	11000	53000	110000	28000
Mixer/Loader/Applicator																			
Backpack	Cattle	0.01 lb ai/gallon	40 gallons	0.015	0.015	0.009	ND	34	34	54	ND	1.7E-04	3.48E-05	1.74E-05	ND	210	1000	2100	ND
Backpack	Swine	0.005 lb ai/gallon		0.007	0.007	0.005		69	69	110		9E-05	1.74E-05	8.7E-06		410	2100	4100	
Manually-pressurized Handwand	Cattle	0.01 lb ai/gallon	40 gallons	0.58	0.003	0.002	ND	0.86	200	240	ND	1.74E-04	3.48E-05	1.74E-05	ND	210	1000	2100	ND
Manually-pressurized Handwand	Swine	0.005 lb ai/gallon		0.146	ND	0.001		1.7	400	470		8.7E-05	1.74E-05	8.7E-06		410	2100	4100	
Mechanical pressurized Handgun	Cattle	0.01 lb ai/gallon	100 gallons	0.026	0.009	0.005	ND	19	54	95	ND	1.14E-03	2.29E-04	1E-04	ND	32	160	320	ND
Mechanical pressurized Handgun	Swine	0.005 lb ai/gallon	100 gallons	0.013	0.005	0.003	ND	38	110	190	ND	5.72E-04	1.14E-04	5.72E-05	ND	63	320	630	ND
Mechanical pressurized Handgun	Cattle	0.01 lb ai/gallon	400 gallons	0.104	0.037	0.021	ND	4.8	13	24	ND	4.58E-03	9.16E-04	4.58E-04	ND	7.9	39	79	ND
Mechanical pressurized Handgun	Swine	0.005 lb ai/gallon	400 gallons	0.052	0.019	0.011	ND	9.6	27	47	ND	2.29E-03	4.58E-04	2.29E-04	ND	16	79	160	ND

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015). PPE represented includes SL= baseline dermal (long sleeved shirt, long pants, shoes and socks), SL/G baseline dermal plus gloves, DL/G= coverall over baseline dermal plus gloves, EC= closed system. NR = no respirator; PF5 = "Protection Factor 5", indicating a reduction in exposure of 80%; PF10 = "Protection Factor 10" indicating a reduction in exposure of 90%.

2 Based on registered coumaphos labels Reg # 11556-115 and 11556-23.

3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1997. EXPOSAC discussion 03/14/2013.

4 Dermal Dose= Dermal Unit Exposure (µg/lbs a.i.) × Application Rate (lbs a.i./acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (kg).

5 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).

6 Inhalation Dose = Inhalation Unit Exposure (µg/lbs a.i.) × Conversion Factor (0.001 mg/µg) × Application Rate (lbs ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (kg).

7 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table 9.1.6. Steady State-Term Duration ARI Occupational Handler Non-Cancer Exposure and Risk Estimates for Liquid Formulations (Reg #s. 11556-115, and 11556-23[1])

Application Equipment	Application Type	Target Animal	Application Rate[2]	Amount Handled / Area Treated[3]	ARI[4]							
					SL/No G + No-R	SL/G + No-R	DL/G + No-R	SL/G + PF5 R	DL/G + PF5 R	SL/G+ PF10 R	DL/G+ PF10 R	EC
Mixer/Loader												
Back Oil Rubbers	Broadcast	Cattle	0.076172 lb ai/ gallon mixture	14 gallons	0.14	0.7	0.85	0.82	1	0.84	1.1	2.7
Mixer/Loader/Applicator												
Backpack	Broadcast	Cattle	0.01 lb ai/gallon	40 gallons	0.023	0.023	0.03	0.031	0.046	0.032	0.05	ND
Backpack	Broadcast	Swine	0.005 lb ai/gallon	40 gallons	0.046	0.046	0.061	0.063	0.095	0.066	0.1	ND
Manually-pressurized Handwand	Broadcast	Cattle	0.01 lb ai/gallon	40 gallons	0.00085	0.052	0.054	0.13	0.14	0.16	0.18	ND
Manually-pressurized Handwand	Broadcast	Swine	0.005 lb ai/gallon	40 gallons	0.0017	0.1	0.11	0.25	0.28	0.31	0.35	ND
Mechanically-pressurized Handgun	Broadcast	Cattle	0.01 lb ai/gallon	100 gallons	0.0068	0.0089	0.0096	0.027	0.034	0.036	0.05	ND
Mechanically-pressurized Handgun	Broadcast	Swine	0.005 lb ai/gallon	100 gallons	0.014	0.018	0.019	0.054	0.068	0.072	0.1	ND
Mechanically-pressurized Handgun	Broadcast	Cattle	0.01 lb ai/gallon	400 gallons	0.0017	0.0022	0.0024	0.0065	0.0084	0.0087	0.013	ND
Mechanically-pressurized Handgun	Broadcast	Swine	0.005 lb ai/gallon	400 gallons	0.0034	0.0045	0.0048	0.013	0.017	0.018	0.025	ND

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015). PPE represented includes SL= baseline dermal (long sleeved shirt, long pants, shoes and socks), SL/G baseline dermal plus gloves, DL/G= coverall over baseline dermal plus gloves, EC= closed system. NR = no respirator; PF5 = "Protection Factor 5", indicating a reduction in exposure of 80%; PF10 = "Protection Factor 10" indicating a reduction in exposure of 90%.

2 Based on registered coumaphos labels Reg # 11556-115 and 11556-23.

3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1997. EXPOSAC discussion 03/14/2013.

4 ARI = Aggregate Risk Index = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)].

Table 9.1.7. Occupational Handler Dermal and Inhalation Unit Exposures for Dust Based Formulations and Impregnated Material

Crop / Target Category		Application Rate[2]	Amount Handled / Area Treated[3]	Dermal Unit Exposures (ug/lb ai)[1]				Inhalation Unit Exposures (ug/lb ai)[1]			
Application Equipment				SL/No G	SL/G	DL/G	EC	No-R	PF5 R	PF10 R	EC
Mixer/Loader											
Dust bag	Small Cattle Farm	0.009615 lb ai/cattle	100 cattle	227	51.6	41.2	ND	8.96	1.792	0.896	ND
Dust bag	Medium Cattle Farm	0.009615 lb ai/cattle	350 cattle	227	51.6	41.2	ND	8.96	1.792	0.896	ND
Dust bag	Large Cattle Farm	0.009615 lb ai/cattle	500 cattle	227	51.6	41.2	ND	8.96	1.792	0.896	ND
Applicator											
Shaker can	Cattle or Horse	0.00125 lb ai/cow or horse	25 Cows or horses	4042000	110000	72600	ND	17500	3500	1750	ND
Shaker can	Swine	0.000625 lb ai/pg	25 pigs	4042000	110000	72600	ND	17500	3500	1750	ND
Shaker can	Swine Bedding	4.17E-05 lb ai/ft2	1000 ft2	4042000	110000	72600	ND	17500	3500	1750	ND
Impregnated Material Non Dust formulations											
Ear Tag[9]	Cattle	20% a.i./tag	Negligible exposure								
Bee Mite Strip[9]	Bee hives	10% a.i./strip	Negligible exposure								

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015). PPE represented includes SL= baseline dermal (long sleeved shirt, long pants, shoes and socks), SL/G baseline dermal plus gloves, DL/G= coverall over baseline dermal plus gloves, EC= closed system. NR = no respirator; PF5 = "Protection Factor 5", indicating a reduction in exposure of 80%; PF10 = "Protection Factor 10" indicating a reduction in exposure of 90%.

2 Based on registered coumaphos dust and solid formulated labels.

3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. Reassessment of Operator Exposure and Risk for the Animal Spray and Dip Uses of Coumaphos June 10, 1997. EXPOSAC discussion 03/14/2013.

Table 9.1.8. Steady State-Term Occupational Handler Non-Cancer Exposure and Risk Estimates for Dust Based Formulations and Impregnated Material[1]

Application Equipment	Crop / Target Category	Application Rate[2]	Amount Handled / Area Treated[3]	Dermal Dose (mg/kg/day)[4]			Dermal MOE[5] (LOC=1000)			Inhalation Dose (mg/kg-day)[6]			Inhalation MOE[7] (LOC=3000)		
				SL/No G	SL/G	DL/G	SL/No G	SL/G	DL/G	No-R	PF5 R	PF10 R	No-R	PF5 R	PF10 R
Mixer/Loader															
Dust bag	Small Cattle Farm	0.009615 lb ai/cattle	100 cattle	0.00316	0.00072	0.0006	160	700	870	1.25E-04	2.49E-05	1.25E-05	290	1400	2900
Dust bag	Medium Cattle Farm	0.009615 lb ai/cattle	350 cattle	0.0111	0.00252	0.0020	45	200	250	4.3E-04	8.74E-05	4.38E-05	82	410	820
Dust bag	Large Cattle Farm	0.009615 lb ai/cattle	500 cattle	0.0158	0.00359	0.0029	32	140	170	6.25E-04	1.25E-04	6.25E-05	58	290	580
Applicator															
Shaker can	Cattle and Horses	0.00125 lb ai/cow or horses	25 Cows or horses	1.83	0.0499	0.0329	0.27	10	15	7.93E-03	1.58E-03	7.93E-04	4.5	23	45
Shaker can	Swine	0.000625 lb ai/pg	25 pigs	0.916	0.0249	0.0164	0.55	20	30	3.96E-03	7.93E-04	3.96E-04	9.1	45	91
Shaker can	Swine Bedding	4.17E-05 lb ai/ft2	1000 ft2	2.43	0.0664	0.0439	0.21	7.5	11	1.06E-03	2.12E-03	1.06E-03	3.4	17	34
Impregnated Material Non Dust formulations															
Ear Tag[9]	Cattle	20% a.i./tag	Negligible exposure												
Bee Mite Strip[9]	Bee hives	10% a.i./strip	Negligible exposure												

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015); Level of mitigation represented in table includes baseline inhalation and additional PPE **required gloves (G) and PF5 respirator.** It is noted that the labels suggests that handlers could utilized more protective equipment however it does not appear to be a requirement on various dust labels.
2 Based on registered coumaphos dust and solid formulated labels
3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. June 10, 1997. Dust bag estimates are best judgments utilizing farm surveys from memo. EXPOSAC discussion 03/14/2013
4 Dermal Dose= Dermal Unit Exposure (µg/lbs a.i.) × Application Rate (lbs a.i./acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (69kg).
5 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lbs a.i.) × Conversion Factor (0.001 mg/µg) × Application Rate (lbs a.i./ gal.) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (69kg).
7 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table 9.1.9. Steady State-Term ARI Occupational Handler Non-Cancer Exposure and Risk Estimates for Dust Based Formulations [1]

Application Equipment	Target Category	Application Rate[2]	Amount Handled / Area Treated[3]	ARI[4]						
				SL/No G + No-R	SL/G + No-R	DL/G + No-R	SL/G + PF5 R	DL/G + PF5 R	SL/G + PF10 R	DL/G + PF10 R
Mixer/Loader										
Dust bag	Small Cattle Farm	0.009615 lb ai/cattle	100 cattle	0.06	0.085	0.087	0.28	0.3	0.41	0.46
Dust bag	Medium Cattle Farm	0.009615 lb ai/cattle	350 cattle	0.017	0.024	0.025	0.081	0.088	0.12	0.13
Dust bag	Large Cattle Farm	0.009615 lb ai/cattle	500 cattle	0.012	0.017	0.017	0.057	0.062	0.081	0.09
Applicator										
Shaker can	Cattle, and Horses	0.00125 lb ai/cow or horse	25 Cows or horses	0.00023	0.0013	0.0014	0.0043	0.0051	0.006	0.0075
Shaker can	Swine	0.000625 lb ai/pg	25 pigs	0.00047	0.0026	0.0028	0.0086	0.01	0.012	0.015
Shaker can	Swine Bedding	4.17E-05 lb ai/ft2	1000 ft2	0.00018	0.00098	0.001	0.0032	0.0037	0.0045	0.0056

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (September 2015); Level of mitigation represented in table includes baseline inhalation and additional PPE **required gloves (G) and at least a PF5 respirator.** It is noted that the labels suggests that handlers could utilized more protective equipment however it does not appear to be a requirement on various dust labels.

2 Based on registered coumaphos dust and solid formulated labels.

3 Exposure Science Advisory Council Policy #9.1.and assumptions from Memo D262059. June 10, 1997. Dust bag estimates are best judgments utilizing farm surveys from memo. EXPOSAC discussion 03/14/2013

4 ARI = Aggregate Risk Index

9.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

9.2.1 Occupational Post-Application Inhalation Exposure

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for coumaphos.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

9.2.2 Occupational Post-Application Dermal Exposure

Dermal post-application exposure is not anticipated due to the limited coumaphos use pattern on livestock and embedded ear and beehive strips, and therefore was not included in this assessment.

Restricted Entry Interval

Coumaphos is classified as Toxicity Category III via the dermal route and Toxicity Category IV for skin irritation potential. It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2) (iii), a.i.'s classified as Acute III or IV for acute dermal, eye irritation and primary skin irrigation are assigned a 12-hour REI. However, in the worker protection standard (WPS) (40 CFR 170.103: Exceptions), there is an exception for pesticides applied "on livestock or other animals, or in or about animal premises." Therefore, coumaphos labels do not fall under WPS. Language on

coumaphos end use product labels should retain statements such as, "Do not contact treated animals until sprays have dried and dusts have settled on the coat."

10.0 Incident Report

One component of the Agency's registration review program is consideration of human observational information including incident data, medical case reports, general medical information, and epidemiology studies. In conjunction with a human health risk assessment based on other data sources, such human incident and other human data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

For the Main Incident Data System (IDS) from January 1, 2009- May 6, 2014, there were 3 incidents reported for coumaphos. One incident was classified as major severity and two were classified as moderate severity. SENSOR-Pesticides identified 5 cases from 1998 to 2010; three involved ingestion, one involved the misapplication of the product (intended for cattle) inside a home. Based on the low frequency and severity of incident cases reported for coumaphos in both IDS and National Institute of Occupational Safety and Health Sentinel Event Notification System for Occupational Risk (NIOSH SENSOR) Pesticides, there does not appear to be a concern at this time that would warrant further investigation. Additionally, the findings of the research reviewed from the Agricultural Health Study do not support any changes to OPP's approach to quantitative risk assessment for coumaphos. However, OPP will continue to monitor the AHS and other epidemiologic results and will re-evaluate these conclusions as needed.

11.0 References

Coumaphos: Acute and Steady State Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments to Support Registration Review. D412870, 02/04/2016, S. Piper.

Addendum to Revised Drinking Water Assessment for the Registration Review of Coumaphos. D420394, 06/02/2014, F. Khan.

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Coumaphos: Updated Tier I Review of Human Incidents for Preliminary Risk Assessment. D413032, 05/27/2014, S. Recore.

Coumaphos: Registration Review Scoping Document for Human Health Assessment. D347381, 02/28/2008, S. Recore.

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Appendix A: Toxicology

A.1 Toxicity Profile

A.1.1: Summary of OPP's ChE Policy & Use of BMD Modeling

OPP's ChE policy (USEPA, 2000[8]) describes the manner in which ChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure (PoD) selected.

AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or cholinesterase (ChE) inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung etc) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and red blood cell, RBC) ChE. Blood measures do not represent the target tissue, per se, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.

Refinements to OPP's use of ChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PoDs for AChE inhibiting compounds. Most often the decreasing exponential empirical model has been used.

OPP does have not a defined benchmark response (BMR) for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity in the brain compartment and is a response level close to the background brain ChE level. With respect to biological considerations, a change in 10% brain AChE inhibition is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC AChE inhibition, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC AChE inhibition but BMRs up to 20% could be considered on a case by case

[8] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.

basis as long as such PoDs are protective for brain AChE inhibition, potential peripheral inhibition, and clinical signs of neurotoxicity.

A.1.2: Results for BMD/BMDL Modeling for Coumaphos

Table A.1.2.1 BMD results of single dose studies.

Coumaphos/Study	Sex/age	Compartment	BMD Results	
			BMD_{10} (mg/kg)	$BMDL_{10}$(mg/kg)
MRID 46258301 CCA Acute Study in Rats – Single Dose (gavage)	Male PND11	RBC	0.36	0.25
	Female PND11	RBC	0.38	0.25
	Male PND11	Brain	0.55	0.46
	Female PND11	Brain	0.59	0.49
MRID 46258301 CCA Acute Study in Rats– Single Dose (gavage)	Adult Male PND 56-70	RBC	0.31	0.19
	Adult Female PND 56-70	RBC	0.57	0.34
	Adult Male PND 56-70	Brain	No inhibition at highest dose tested of 4 mg/kg/day; No reliable fit (g)	
	Adult Female PND 56-70	Brain	No inhibition at highest dose tested of 4 mg/kg/day; No reliable fit (g)	

Table A.1.2.2: BMD results of repeated dosing studies ranging in duration from 11 days to 1 year.

Coumaphos/Study	Sex/age	Compartment	BMD Results	
			BMD_{10} (mg/kg)	$BMDL_{10}$(mg/kg)
MRID 46502201 CCA Repeat Study in Rats– 11 days (gavage)	Pup Male PND11	RBC	0.057	0.041
	Pup Female PND11	RBC	0.052	0.042
	Pup Male PND11	Brain	0.337	0.237
	Pup Female PND11	Brain	0.528	0.278
	Adult Male PND 56-70	RBC	0.127	0.089
	Adult Female PND 56-70	RBC	0.106	0.085
	Adult Male PND 56-70	Brain	No inhibition at highest dose tested of 0.98 mg/kg/day; No reliable fit (g)	
	Adult Female PND 56-70	Brain	No inhibition at highest dose tested of 0.98 mg/kg/day; No reliable fit (g)	

Table A.1.2.2: BMD results of repeated dosing studies ranging in duration from 11 days to 1 year.				
Coumaphos/Study	**Sex/age**	**Compartment**	**BMD Results**	
			BMD_{10} (mg/kg)	**$BMDL_{10}$(mg/kg)**
MRID 43055301 – Subchronic (91 day) Dog (diet)	Male	RBC	0.17	0.104
	Female	RBC	0.17	0.15
MRID 43055301 – Chronic (1 yr) Dog (diet)	Male	Brain	1.36	0.77
	Female	Brain	1.30[a]	0.52[a]
MRID 45912101 – Developmental Neurotoxicity in Rats (Diet)	Male Pup PND21	RBC	1.50	0.11
	Female Pup PND21	RBC	0.61	0.28
	Male Pup PND21	Brain	6.70	2.86
	Female Pup PND21	Brain	3.18	1.86
	Maternal lactational day 21 (gestation and lactation) (~42D of dosing)	RBC	0.08[b]	0.03[b]
	Maternal lactational day 21 (gestation and lactation) (~42D of dosing)	Brain	0.68	0.53
MRID 44775901 – Subchronic Neurotoxicity Study in Rats (diet)	Male 4 weeks of dosing	RBC	0.096	0.085
	Female 4 weeks of dosing	RBC	0.085	0.073
	Male 14 weeks of dosing	RBC	0.11	0.082
	Female 14 weeks of dosing	RBC	0.25	0.20
	Male 14 weeks of dosing	Brain	Poor dose-response	Poor dose-response
	Female 14 weeks of dosing	Brain	1.997	1.29
MRID - 00126526 90 Day Rat Study (1983) (Diet)	Male 8 weeks of dosing	RBC	0.16	0.1
	Female 8 weeks of dosing	RBC	0.17	0.14
	Male 13 weeks of dosing	RBC	0.15	0.12
	Female 13 weeks of dosing	RBC	0.1 (f)	0.08 (f)
	Male 13 weeks of dosing	Brain	1.05	0.58
	Female 13 weeks of dosing	Brain	Poor dose-response	Poor dose-response
MRID – 43061701	Male – F0	RBC	No reliable fit	No reliable fit

Table A.1.2.2: BMD results of repeated dosing studies ranging in duration from 11 days to 1 year.				
Coumaphos/Study	**Sex/age**	**Compartment**	**BMD Results**	
			BMD_{10} (mg/kg)	**$BMDL_{10}$(mg/kg)**
2 generation reproduction study in rats– 91 days (Diet)	Female – F0	RBC	0.07[c]	0.04[c]
	Male – F0	Brain	Poor dose-response(no brain AChEI in males at highest dose tested of 1.79 mg/kg/day)	Poor dose-response
	Female – F0	Brain	Poor dose-response	Poor dose-response
	Male – F1	RBC	0.048	0.036 (rounded to 0.04)
	Female – F1	RBC	0.050	0.036 (rounded to 0.04)
	Male – F1	Brain	7.55 (no brain AChEI in males at highest dose tested of 1.79 mg/kg/day)	1.86
	Female – F1	Brain	1.75	0.71

Table A.1.2.3 BMD results of repeated exposure studies via the dermal route for Coumaphos.				
Coumaphos Study	**Sex/age**	**Compartment**	**BMD Results (mg/kg/day)**	
			BMD_{10}	**$BMDL_{10}$**
MRID 42084901 21-Day Dermal Toxicity Study	Male	Brain	7.53	5.94
	Female	Brain	6.80	5.46
MRID 42084901 21-Day Dermal Toxicity Study	Male	RBC	1.24[d]	1.06[d]
	Female	RBC	0.82[e]	0.71[e]
MRID 42666401 21-Day Dermal Toxicity Study (h)	Female	RBC	0.72	0.50
	Female	Brain	No inhibition observed at highest dose tested	No inhibition observed at highest dose tested

[a] p=0.09 for model fit; based on visual inspection and supporting results from Chronic Dog Male Brain, this model fit is adequate.
[b] p=0.03 for model fit; based on visual inspection and taking into account the observed dose spacing issues, this model fit is adequate and these results are reported for characterization purposes.
[c] Based on visual inspection and taking into account the observed dose spacing issues, this model fit is adequate and these results are reported for characterization purposes.
[d] p=0.07 for model fit; based on visual inspection, this model fit is adequate.
[e] p=0.08 for model fit; based on visual inspection, this model fit is adequate.
[f] p=0.09 for model fit; based on visual inspection and supporting RBC male 13 week results, this model fit is adequate and these results are reported for characterization purposes.
[g] BMD10 outside dose range and therefore is unreliable.
[h] Only females evaluated in this dermal study.

A.2: Toxicology Profile and Executive Summaries

A.2.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for coumaphos are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.2.1.1 Toxicology Data Requirement for Coumaphos

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Acute Eye Irritation	yes	yes
870.2500	Acute Dermal Irritation	yes	yes
870.2600	Skin Sensitization	yes	yes
870.3100	90-Day Oral Toxicity in Rodents	yes	yes
870.3150	90-Day Oral Toxicity in Non rodents	yes	yes
870.3200	21/28-Day Dermal Toxicity	yes	yes
870.3250	90-Day Dermal Toxicity	yes	yes
870.3465	90-Day Inhalation Toxicity	yes	no
870.3700a	Prenatal Developmental Toxicity (rodent)	yes	Yes
870.3700b	Prenatal Developmental Toxicity (Non rodents)	yes	yes
870.3800	Reproduction and Fertility Effects	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	Yes
870.4100b	Chronic Toxicity (Non rodents)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	yes	yes
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes
870.7485	Metabolism and Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes

CR- conditionally required

A.2.2 Toxicity Profiles

Table A.2.2.1 Acute Toxicity Profile of Coumaphos				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [rat]	00110597	LD_{50} (M) >240 mg/kg LD_{50} (F) = 17 mg/kg	I
870.1200	Acute dermal [rabbit]	00110598	LD_{50}: >2400 mg/kg	III
870.1300	Acute inhalation [rat]	00110601	LC_{50} (M) = 1.081 mg/L LC_{50} (F) = 0.341 mg/L	II
870.2400	Acute eye irritation [rabbit]	00110599	Mild Irritant, resolved by day 7	IV
870.2500	Acute dermal irritation [rabbit]	00110600	No Irritation	IV
870.2600	Skin sensitization [guinea pig]	00110602	Non sensitizer	N/A

Table A.2.2.2 . Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90 day oral rat (Diet)	MRID 00126527 (1983) guideline/acceptable 0, 2, 5 and 10 ppm equivalent to 0. 0.2, 0.5 and 1 mg/kg/day	RBC AChEI: BMD_{10} = 0.15/0.10 mg/kg/day for males/females **$BMDL_{10}$** = 0.12/0.08* mg/kg/day for males/females (*=p=0.09 for model fit for female data; based on visual inspection and supporting male RBC data this model fit is adequate and reported for characterization) Brain AChEI: BMD_{10} = 1.05 mg/kg/day for males; poor dose-response for females **$BMDL_{10}$**= 0.58 mg/kg/day for males; poor dose-response for females NOAEL= not observed LOAEL= 0.2 mg/kg/day (2 ppm) based on 18-32% RBC AChE inhibition

Table A.2.2.2 . Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3250 21-Day Dermal Rat Toxicity	MRID 42084901 Acceptable guideline when considered with 21 dermal study (MRID 42666401, below) 0, 2, 4, 20 or 100 mg/kg/day	<u>RBC AChE inhibition:</u> BMD_{10}=1.24(a)/0.82(b) mg/kg/day for males/females BMD_{L10}= 1.06(a)/0.71 (b) mg/kg/day for males/females (a) P=0.07 for model fit; based on visual inspection this model fit is adequate (b) P=0.08 for model fit; based on visual inspection this model fit is adequate <u>Brain AChE inhibition:</u> BMD_{10}= 7.53/6.8 mg/kg/day for males/females $BMDL_{10}$= 5.94/5.46 mg/kg/day for males/females NOAEL= not identified (< 2 mg/kg/day) LOAEL=< 2 mg/kg/day based on 14% and 20% RBC AChEI in females and males, respectively.
870.3250 21-Day Dermal Rat Toxicity	MRID 42666401 Acceptable guideline when considered with 21 day dermal study (MRID 42084901, above) 0, 0.1, 0.5, 1.1, or 2.1 mg/kg/day in females only	<u>RBC AChE inhibition:</u> BMD_{10}=0.72 mg/kg/day for females BMD_{L10}= 0.5 mg/kg/day for females Brain AChE inhibition: No inhibition at the highest dose tested NOAEL= 1.1 mg/kg/day LOAEL = 2.1 mg/kg/day based on 28% RBC CheI.
2- and 5-Day Dermal Toxicity in Rats	MRID 44749401 (1999) Acceptable non-guideline 0, 2.5, 5, 10 , 20 and 50 mg/kg in females only	5-Day NOAEL= 5 mg/kg LOAEL= 10 mg/kg based on 12% brain ChE inhibition 2-Day NOAEL = 20 mg/kg LOAEL= 50 mg/kg based on brain, plasma and RBC ChE inhibition
870.3700a Prenatal developmental in (rodent)	MRID 00131684 (1983) Acceptable guideline 0, 1, 5, or 25 mg/kg from GD 6 to 15	**Maternal** NOAEL = 5 mg/kg/day LOAEL =25 mg/kg/day based on tremors. **Developmental** NOAEL > 25 mg/kg/day LOAEL = no effects noted AChE not measures in dams or fetuses.
870.3700b Prenatal developmental in (Non rodents)	MRID 00131683 (1983) Acceptable guideline 0, 0.25, 2, or 18 mg/kg from GD 7 to 19	**Maternal** NOAEL = 2 mg/kg/day LOAEL =18 mg/kg/day based on mortality (2/17) and cholinergic signs. **Developmental** NOAEL > 18 mg/kg/day LOAEL = no effects noted AChE not measures in dams or fetuses.

Table A.2.2.2 . Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800 Reproduction and Fertility Effects (Diet)	MRID 43061701 (1993) Acceptable guideline 0, 1, 5 and 25 ppm (F1 females: 0, 0.08, 0.34, 2.02 mg/kg/day; F1 males: 0, 0.07, 0.3, 1.79 mg/kg/day)	**Parental/Systemic** RBC AChEI BMD_{10} / $BMDL_{10}$ = 0.07/0.04 (c) for females; no reliable fit for males Brain ChEI BMD_{10} / $BMDL_{10}$ = poor dose response (~~males~~/females) however, at 1.79/2.02 mg/kg/day brain AChEI was 30% in females. No brain AChEI in males at highest dose tested. (c) based on visual inspection and taking into account the observed dose spacing this model fit is adequate and reported for characterization. **Reproductive** NOAEL =25 ppm (2.02/1.79 mg/kg/day) highest dose tested (HDT) mg/kg/day LOAEL = not established **Offspring** RBC AChEI: BMD_{10} = 0.048/0.05 mg/kg/day (F1 males/females); $BMDL_{10}$ 0.036 mg/kg/day (F1 males and females at 91 days) Brain AChEI : BMD_{10} = 7.55/1.75 mg/kg/day for males/females; $BMDL_{10}$ = 1.86/0.71 mg/kg/day for males/females. No brain AChEI in F1 or F2 males at highest dose tested
870.4100b Chronic toxicity (dog) (Diet)	43055301 (1993) Acceptable guideline both studies together 0, 1, 30 or 90 ppm (0, 0.025, 0.775 and 2.3 mg/kg/day in males and 0.024, 0.7 and 2.5 mg/kg/day in females).	RBC AChE inhibition: BMD_{10} = 0.17 mg/kg/day for males and females **$BMDL_{10}$** = 0.104/0.15 mg/kg/day for males/females (90 day measurement which reached steady state) Brain AChE inhibition: BMD_{10} =1.36/1.3 (d) mg/kg/day for males/females **$BMDL_{10}$** = 0.77/0.52 (d) mg/kg/day for males/females (d) p=0.09 for model fit, based on visual inspection and supporting results from chronic male brain data, this model fit is adequate and reported for characterization. NOAEL = 0.025 mg/kg/day LOAEL = 0.7 mg/kg/day based on significant and biologically relevant depression of RBC and plasma ChE activity. (RBC AChEI was 53-63% for males, and 51-66% for females).
870.4200b Carcinogenicity (mouse) (Diet)	05009938 (1979) Acceptable guideline 0, 10 or 20 ppm	No clinical signs. No evidence of oncogenicity. No AChE measurements were made.

Table A.2.2.2 . Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300 Combined Chronic Toxicity/Carcinogenicity in rat (Diet)	MRID 40836001 (1988) Acceptable guideline 0, 1, 5 or 25 ppm coumaphos (0, 0.07, 0.36 or 1.7 mg/kg/day)	NOAEL = 0.36 mg/kg/day LOAEL = 1.7 mg/kg/day based on decreased RBC activity in both males and females, and decreased body weight gain in females.
Gene Mutation 870.5100	MRID 00131681 Acceptable guideline	In a Pol A1 test on E. coli there was no evidence of mutagenicity.
Gene Mutation 870.5375	MRID 00131680 Acceptable guideline	In salmonella/microsome assay coumaphos was inactive when tested either with or without liver microsomal enzyme preparations.
in vivo test for interaction with Gonadal DNA chromosomal aberration	MRID 41847501 Acceptable guideline	No demonstration of mutagenic activity at 480 mg/kg.
870.6200a Acute Neurotoxicity Screening Battery	MRID 44544801 (1998) Acceptable guideline 0, 2, 75 and 250 mg/kg	NOAEL = not identified LOAEL =2 mg/kg/day based on significant RBC and plasma AChE inhibition.
870.6200b Subchronic Neurotoxicity Screening Battery (Diet)	MRID 44775901 (1998) Acceptable guideline 0, 1, 15 or 75 ppm coumaphos equivalent to 0, 0.07, 0.99 and 5 mg/kg/day for males, and 0, 0.08, 1.15, and 6 mg/kg/day for females	RBC AChE inhibition: BMD_{10} = 0.11/0.25 mg/kg/day for males/females **$BMDL_{10}$** = 0.082/0.2 mg/kg/day for males/females Brain AChE inhibition: BMD_{10} = 1.997 mg/kg/day for females **$BMDL_{10}$** = 1.29 mg/kg/day for females (poor dose response for males) NOAEL = 0.07 mg/kg/day for males and 0.08 mg/kg/day for females LOAEL =0.99/1.15 mg/kg/day for males and females, respectively based on 55-64% and 41-75% RBC inhibition, respectively.

Table A.2.2.2 . Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.6300 Developmental Neurotoxicity (Diet)	MRID 45912101 (2003) Acceptable non-guideline pending review of positive control data 0, 1, 5 or 30 ppm in diet from gestation day 0 through PND 21 equivalent to 0, 0.09, 0.47. 2.77 mg/kg during gestation and 0, 0.22, 1.06 and 7.4 mg/kg/day during lactation	**Maternal at LD21** RBC AChE inhibition: BMD_{10} = 0.08 mg/kg/day (e) **$BMDL_{10}$** = 0.03 mg/kg/day (e) Brain AChE inhibition: BMD_{10} = 0.68 mg/kg/day **$BMDL_{10}$** = 0.53 mg/kg/day (e) p=0.03 for model fit based on visual inspection and taking into account the observed dose spacing this model fit is adequate and reported for characterization 21% plasma and 78% RBC AChEI observed at 0.47 mg/kg/day **Offspring** RBC AChE inhibition: BMD_{10} = 1.5/0.61 mg/kg/day for males/female PND 21 pups **$BMDL_{10}$**= 0.11/0.28 mg/kg/day for males/female PND 21 pups Brain AChE inhibition: BMD_{10} = 6.7/3.18 mg/kg/day for male/female PND 21 pups **$BMDL_{10}$** = 2.86/1.86 mg/kg/day for male/female PND 21 pups NOAEL = 0.47 mg/kg/day LOAEL = 2.77 mg/kg/day based on morphometric changes in the brain of PND21 males and inhibition of 27-30% plasma, 19-33% RBC and 4-8% brain cholinesterase activity.
870.7485 Metabolism and Pharmacokinetics	MRID 00138596 (1983)	Coumaphos labeled on the leaving group was rapidly excreted as a conjugate n the urine. There were no dose-related changes in metabolism and no evidence of activation or bioaccumulation of the leaving group.
870.7800 Immunotoxicity	MRID 48325701 Acceptable Guideline	Immunotoxicity NOAEL= 6.45/6.59 mg/kg/day (M/F) (Highest dose tested). LOAEL not established
Special studies Comparative Cholinesterase Assay (CCA)—Acute in Rat	MRID 46258301 Acceptable non-guideline Adults: 1, 2, or 4 mg/kg; PND 11 pups: 0.25, 0.5, or 1 mg/kg	Adults: RBC AChE inhibition peak 8 hours BMD_{10} = 0.31/ 0.57 mg/kg for males/females **$BMDL_{10}$** = 0.19 / 0.34 mg/kg for males/females Brain AChE inhibition outside range of dosing and no reliable fit. No brain inhibition at highest dose tested. PND 11 pups: RBC AChE inhibition peak 4 hours BMD_{10} = 0.36/0.38 mg/kg for males/females **$BMDL_{10}$** = 0.25 mg/kg for both males/females Brain AChE inhibition peak 4 hours: BMD_{10} = 0.55/0.59 mg/kg for males/females **$BMDL_{10}$** = 0.46/0.49 mg/kg for males/females

Table A.2.2.2 . Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Special studies Comparative Cholinesterase Assay (CCA) in Rat 11-Day Repeat Dosing (Gavage)	MRID 46502201 (2005) unacceptable non-guideline Adults: 0, 0.2, 0.49, 0.98 PND11 pups: 0, 0.19, 0.46, 0.7 mg/kg/day	Adults: RBC AChE inhibition BMD_{10} = 0.127/0.106 mg/kg for males/females and **$BMDL_{10}$** = 0.089/0.0847 mg/kg for males/females Brain ChE Inhibition: no reliable fit (BMD10 value outside dose range). No inhibition at 0.98 mg/kg/day (HDT) Blood samples collected 4 hour post dosing. PND 11 Pups: RBC AChE inhibition: BMD_{10} = 0.057/0.052 mg/kg for males/females and **$BMDL_{10}$** = 0.041/0.042 mg/kg for males/females Brain AChE Inhibition: BMD_{10} = 0.34/0.53 mg/kg for males/females and **$BMDL_{10}$** = 0.24/0.28 mg/kg for males/females Blood samples collected 8 hours post-dosing
Special studies Comparative Cholinesterase Assay (CCA) Gestational Dosing (Diet)	MRID 46295201 (2004) unacceptable non-guideline 0, 1, 5, 30 ppm in diet to pregnant rats on GD 0-20 Equivalent to 0, 0.08, 0.41, and 2.62 mg/kg/day	Dams at GD 20: NOAEL: 0.08 mg/kg/day LOAEL: 0.41 mg/kg/day based on 19% RBC AChE inhibition BMD modeling not performed because DNT more sensitive with 78% RBC AChE inhibition at 0.41 mg/kg/day Fetus: NOAEL: 0.41 mg/kg/day LOAEL: 2.62 mg/kg/day based on 22% RBC AChE inhibition
Acute Neurotoxicity in Hen	00115167 Acceptable guideline 22.7 mg/kg	Coumaphos-treated hens remained normal throughout the observation period and showed no histological signs of neurotoxicity. TOCP treated hens developed signs of neurotoxicity, and histopathological evidence of neurotoxicity.

A.3: Hazard Identification and Toxicity Endpoint Selection

Acute Reference Dose (aRfD) – All Populations

Study Selected: Comparative cholinesterase (ChE) study in rats
MRID Number: 46258301
Dose and Endpoint for Establishing aRfD: 0.19 mg/kg (BMDL10), based on 10% RBC ChE inhibition in adult males.
Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factor:
The acute dietary endpoint for the general population is based on the BMDL10 for RBC AChE inhibition (measured at time of peak inhibition) in adult males following a single oral dose in the comparative AChE study. This endpoint is considered appropriate for all populations because the effects were observed following a single dose, and the route of administration (oral) is appropriate for dietary considerations. The BMDL10 is protective of RBC AChE inhibition in PND11 pups, as the BMDL10 for pups is 0.25 mg/kg. (See Table A.2.3).

Steady State Reference Dose (ssRfD)

Study Selected: 2-Generation Reproductive Study in rats
MRID Number: 43061701
Dose and Endpoint for Establishing ssRfD: 0.04 mg/kg (BMDL10), based on 10% RBC ChE inhibition in both male and female F0 and F1 generations rats at 91 days.
Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factor:
The steady state dietary endpoint is based on RBC ChE inhibition in F0 and F1 generation males and females in the 2 generation reproductive study in rats. This endpoint is considered appropriate for steady state dietary exposure due to the oral route of administration and the chronic duration of exposure. The study and endpoint were selected because they are protective of effects observed in all the other available studies for all lifestages, including offspring effects seen in the DNT study, and RBC ChE inhibition in the pups of the CCA study.

Dermal Absorption

Since a dermal toxicity study is the basis of dermal points of departure (PoD), a dermal absorption factor is not required.

Dermal Exposure (Steady State)

Study Selected: 21 Day Dermal study in rats
MRID Number: 42666401
Dose and Endpoint for Establishing dermal PoD: 0.5 mg/kg ($BMDL_{10}$), based on 10% RBC ChE inhibition in adult females (BMD_{10} = 0.72 mg/kg/day).
Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factor:
The steady state dermal endpoint is based on RBC ChE inhibition in female rats in at 21 day dermal toxicity study.

Inhalation Exposure (Steady state)

Study Selected: 2-Generation Reproductive Study in rats
MRID Number: 43061701
Dose and Endpoint for Establishing ssPoD: 0.04 mg/kg (BMDL10), based on 10% RBC ChE inhibition in both male and female F0 and F1 generation rats at 91 days.
Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X database factor for missing inhalation study)
Comments about Study/Endpoint/Uncertainty Factor:
The steady state inhalation endpoint is based on RBC ChE inhibition in F0 and F1 generation males and females in the 2 generation reproductive study in rats. The study and endpoint were selected because they are protective of effects observed in all the other available studies for all lifestages, including offspring effects seen in the DNT study, and RBC ChE inhibition in the pups of the CCA study. In the absence of absorption data, it is assumed that inhalation absorption is 100% (equivalent) to oral absorption.

A.4: Executive Summaries for Studies Selected as Basis of PoDs

a. Acute Comparative Cholinesterase Assay (CCA)

The relative sensitivities to ChE inhibition at peak inhibition by coumaphos were measured in neonatal and young adult Wistar rats (MRID 46258301). In these studies, coumaphos was administered in a single gavage dose of 0, 0.25, 0.50, or 1.0 mg/kg/day to neonatal (postnatal day 11) rats and of 0, 1.0, 2.0 or 4.0 mg/kg/day to young adult (postnatal day 58-63) rats. Peak ChE inhibition was measured 8 or 4 hours following dosing to young adult or neonatal rats, respectively. In young adults, doses of 1.0/2.0 mg/kg resulted in plasma (male/females=33%/38%) and erythrocyte (males/females=34%30%) ChE inhibition. Brain ChE activities were not inhibited at any dose level in males or females. In neonates, the NOAEL/LOAEL was 0.25/0.5 mg/kg based on plasma (males/females 19%/22%), erythrocyte (males /females 20%/19%), and brain (8%/7%) ChE inhibition. The study shows that coumaphos treatment of PND 11 male and female pups by a single gavage dose results in ChE inhibition at a lower dose than similar treatment of PND 58-63 male and female young adults. In addition, brain ChE was inhibited at the same LOAEL as plasma and erythrocyte ChE in male and female neonatal pups, whereas young adults showed no brain ChE inhibition at any dose level in males or females. Therefore, this comparative ChE study does demonstrate increased quantitative susceptibility of the offspring.

For adults, the RBC ChE inhibition BMD$_{10}$ = 0.31/ 0.57 mg/kg for males/females, and the **BMDL$_{10}$** = 0.19 / 0.34 mg/kg for males/females. Brain ChE inhibition outside range of dosing and no reliable fit of these data. For PND 11 pups RBC ChE inhibition BMD10 = 0.36/0.38 mg/kg for males/females, and the **BMDL$_{10}$** = 0.25 mg/kg for both males/females. For brain ChE inhibition the BMD$_{10}$ = 0.55/0.59 mg/kg for males/females, while the **BMDL$_{10}$** = 0.46/0.49 mg/kg for males/females

b. Reproductive Toxicity

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Coumaphos at 0, 1, 5 or 25 ppm (0, 0.07, 0.3, or 1.79 mg/kg/day in males and 0, 0.08, 0.34 or 2.02 mg/kg/day in females, respectively). There was no increased sensitivity to pups over the adults. For parental/systemic toxicity, the NOEL was 25 ppm (1.79 mg/kg/day, (HDT); a LOEL was not established. For reproductive toxicity, the NOEL was 25 ppm (1.79 mg/kg/day); a LOEL was not established (MRID No. 430611701).

In the reproduction study, ChE activity was measured in adults and pups. There was dose-related decreases in plasma and red blood cell cholinesterase activity in dams at 5 and 25 ppm. Generally, no differences were seen on day 47 and day 91 measurements. Brain levels were biologically significantly inhibited (30%) in F_o and F_1 adult females at 25 ppm, and in F_o adult males at 25 ppm. In pups, no significant changes in red blood cell or brain cholinesterase activity were seen on day 4, but on day 21 changes were seen at 25 ppm. In F_1 pups, plasma and red blood cell ChE inhibition of 38-44% was seen, while in F_2 pups, only plasma was affected (31-44%). The only significant brain inhibition in pups was an 8% decrease in F_1 females on

day 21. The NOEL was 5 ppm for cholinesterase inhibition in dams and in pups on day 21 (MRID No. 430611701).

For parental F0 animals, the RBC ChEI BMD_{10} / $BMDL_{10}$ are 0.07/0.04 mg/kg/day, and there was no reliable fit for males. For female RBC data, the BMDs did not provide statistically acceptable results with a P-value of 0.05 using a log-likelihood ratio test for RBC AChE inhibition; however, visual observation of the data show good fit and similar findings to the F1 generation data in the study. The brain AChE data could not be modeled for BMDs due to poor dose response in both males and females.

For F1 offspring, the RBC ChEI BMD_{10} = 0.048/0.05 mg/kg/day (F1 males/females); $BMDL_{10}$ 0.036 mg/kg/day (F1 males and females at 91 days). The Brain ChEI BMD10 = 7.55/1.75 mg/kg/day for males/females; $BMDL_{10}$= 1.86/0.71 mg/kg/day for males/females.

c. 21-day dermal study in the rat (83-2); two studies

1. MRID 42084901

Executive Summary: In a 21-day dermal study coumaphos was administered to 6 male and female Sprague-Dawley [Sas: CD (SD) BR] rats per group at doses of 0, 2, 4, 20 or 100 mg/kg/day for 21 days.

At 2 mg/kg/day (LDT) there was erythrocyte cholinesterase (RBC ChE) inhibition in males (20, 24, 84 and 96 % from low to high dose) and females (14, 42, 89 and 95 % from low to high dose) and plasma ChE inhibition in females (38, 38, 65 and 91 % from low to high dose). At 20 and 200 mg/kg/day plasma (males - 44, 78 % for the 2 high doses) and brain ChE were decreased in males (22 and 59 % for 2 highest doses) and females (26 and 67 % for 2 highest doses).

The BMD_{10}= for RBC AChE inhibition is 1.24/0.82 mg/kg/day for males/females, respectively while the $BMDL_{10}$ is 1.06/0.71 mg/kg/day for males/females. Although the BMD model fit is p=0.07, the Agency determined this model fit is adequate based on visual inspection of the data and consideration of BMDs from MRID 42666401 (see below). **The BMD_{10}= for brain AChE inhibition is 7.53/6.8 mg/kg/day for males/females, respectively while the $BMDL_{10}$ is 5.94/5.46 mg/kg/day for males/females.**

Signs of systemic toxicity occurred at 20 mg/kg/day and above and included muscle fasciculation in males (17 and 67 % for 2 high doses) and females (17 and 100 % for 2 high doses) sporadically throughout the study. Tremors occurred in females (17 and 83 %) after the first week and there were anal stains in males. At 100 mg/kg/day there was increased incidence of hypothermia and activity in females and decreased body weight gains in males and females. The systemic LOAEL is 20 mg/kg/day based on muscle fasciculation and tremors. The systemic NOAEL is 4 mg/kg/day.

This study is classified as core-supplementary data (a NOEL for ChE was not determined) when considered alone and is not acceptable for regulatory purposes. However, the study is considered

core-minimum when taken together with a second study conducted using lower doses in females (MRID 42666401).

2. MRID 42666401

Executive Summary: In a 21-day dermal study coumaphos (was administered to 5 female Sprague-Dawley [Sas: CD (SD) BR] rats per group at doses of 0, 0.1, 0.5, 1.1 or 2.1 mg/kg/day for 21 days.

At 1.1 mg/kg/day RBC ChE was inhibited (24 and 28 % for 2 high doses). **The BMD_{10}= for RBC AChE inhibition is 0.72 mg/kg/day for females, while the BMD_{L10}= 0.5 mg/kg/day for females.** No brain ChE inhibition was noted at the highest dose tested of 2.1 mg/kg/day.

There was no systemic toxicity observed at any dose. The systemic LOAEL is greater than 2.1 mg/kg/day. The systemic NOAEL is 2.1 mg/kg/day (4 mg/kg/day based on a separate study).

This study (MRID 42666401) is considered core-minimum when taken together with study #1

Appendix B: Physical/Chemical

Appendix B.1: Physical/Chemical Properties.

Table B.1: Physicochemical Properties of Technical Grade Coumaphos.		
Parameter	**Value**	**Reference**
Melting Point/Range	90-95°C	DP #207352, Chris Olinger, 12/12/1994
pH	Not available	
Specific Gravity	1.47	Occupational Health Services MSDS for Coumaphos, 2/12/1991
Water Solubility (20°C)	2.0 mg/100 mL	DP #207352, Chris Olinger, 12/12/1994
Solvent Solubility (g/100 mL at 20°C)	Acetone 23.82 Diethyl phthalate 21.50 Ethanol 0.9 Xylene 0.9 Octanol 0.13 Mineral spirits 0.09 Hexane 0.07	
Vapor Pressure (20°C)	0.013 mPa/9.7 x 10^{-8} mm Hg	
Henry's Law constant	3.1 x 10^{-8}	
Dissociation Constant (pK_a)	Not required	
Octanol/Water Partition Coefficient (Log[K_{OW}])	Not available	
UV/Visible Absorption Spectrum	Not available	

Appendix B.2: International Residue Limits for Coumaphos

Table B.2: International Residue Limits for Coumaphos				
US		**Canada**	**Mexico[2]**	**Codex**
Residue Definition:				
40CFR180.189 Coumaphos (O,O -diethyl O -3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphorothioate and its oxygen analog (O,O -diethyl O -3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphate)		Livestock: O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl phosphorothioate, including the oxygen analog O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl phosphate (calculated on the fat content) Honey, honeycomb, beeswax: O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl phosphorothioate, including the oxygen analog O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl phosphate		None (withdrawn 1980)
Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg)				
Commodity	US	Canada	Mexico	Codex
Cattle, fat	1.0	0.5[1]		
Cattle, meat	1.0	0.5[1]		
Cattle, meat byproducts	1.0	0.5[1]		
Goat, fat	1.0	0.5[1]		
Goat, meat	1.0	0.5[1]		
Goat, meat byproducts	1.0	0.5[1]		
Hog, fat	1.0	0.5[1]		
Hog, meat	1.0	0.5[1]		
Hog, meat byproducts	1.0	0.5[1]		
Honey	0.15	0.02		
Honeycomb	45.0	0.1		
Horse, fat	1.0	0.5[1]		
Horse, meat	1.0	0.5[1]		
Horse, meat byproducts	1.0	0.5[1]		
Milk, fat (=n in whole milk)	0.5			
Sheep, fat	1.0	0.5[1]		
Sheep, meat	1.0	0.5[1]		
Sheep, meat byproducts	1.0	0.5[1]		
MRLs with NO US Equivalent				
Beeswax		1		
Fat of poultry		0.5[1]		
Meat-by-products of poultry		0.5[1]		
Meat or poultry				
Completed by M. Negussie; 05/21/14				

[1] Calculated on the fat content.
[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix C: Summary of Occupational Non-Cancer Algorithms

Potential daily exposures for occupational handlers are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$

Where:

E = exposure (mg ai/day),
UE = unit exposure (µg ai/lbs ai),
AR = maximum application rate according to proposed label (lbs ai A or lbs ai/gal), and
A = area treated or amount handled (e.g., A/day, gal/day).

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

Where:

ADD = average daily dose absorbed in a given scenario (mg ai/kg/day),
E = exposure (mg ai/day),
AF = absorption factor (dermal and/or inhalation), and
BW = body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each application handler scenario are calculated using a Margin of Exposure (MOE), which is a ratio of the toxicological endpoint to the daily dose of concern. The daily dermal and inhalation dose received by occupational handlers are compared to the appropriate PoD (i.e., $BMDL_{10}$) to assess the risk to occupational handlers for each exposure route. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

Where:

MOE = margin of exposure: value used by HED to represent risk estimates (unitless),
PoD = point of departure (mg/kg/day), and
ADD = average daily dose absorbed in a given scenario (mg ai/kg/day).
$BMDL_{10}$ = bench mark dose limit.

The aggregate risk index (ARI) was calculated as follows:

Aggregate Risk Index (ARI) = $1 \div (1 \div RI_{dermal}) + (1 \div RI_{inhalation})$

Where:
Risk Index (RI) = MOE ÷ LOC

Appendix D: Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database (PHED) 1.1, and the Agricultural Handler Exposure Task Force (AHETF) database, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[9].

[9] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure